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Effects of Tai Chi on the Protracted Abstinence Syndrome: A Time Trial Analysis

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Abstract: While exercise has been shown to reduce the negative effects of substance withdrawal symptoms, no research has investigated if Tai Chi, a traditional Chinese exercise, has similar effects. Here, we observed the physiological effects of Tai Chi on protracted abstinence syndrome (PAS) in female heroin addicts by comprehensively inspecting their immune system function, complete blood count, hepatic function and renal function. To determine the psychological effects, we used the Hamilton Rating Scale for Depression (HRSD) and the rating scale of heroin withdrawal symptoms. We recruited 70 heroin-addicted young women beginning to undergo withdrawal and randomly assigned them into two groups: one group received one-hour Tai Chi exercise every two days (Tai Chi group, $n = 36$) and the other group did not (control group, $n = 34$). Thirty-three patients finished this six-month trial. Numerous significant physiological differences were observed between all heroin-addicted subjects ($n = 70$) and age-matched healthy individuals ($n = 18$), suggesting a deleterious effect of drug addiction. There were improvements for certain physical parameters between the Tai Chi group ($n = 17$) and the control group ($n = 16$), although the differences were not statistically significant. We observed a small significant difference in psychological effects near the 60-day mark between the two groups. Taken together, our results suggest that Tai Chi might have a positive effect on PAS, which future

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studies can confirm by using an expanded sample size, longer trial time, and more sensitive and specific indicators of psychological and physiological health.

Keywords: Tai Chi; Heroin Addiction; Protracted Abstinence Syndrome; Physical Parameters; HRSD.

Introduction

Morphine, heroin and their derivatives — often called opioids — are widely consumed by substance abusing populations, causing deep dependency. The mechanism of this dependence is complicated. To date, the most accepted theory is adaptation of brain to exogenous opioids that act on the same receptor of endogenous neural transmitters such as endorphins and dopamine, which function as crucial signal molecules in the brain's reward circuit and in formation of habit and long-term memory. From this perspective, opioid dependence can easily be thought of as a kind of "chronic brain disease" (Leshner, 1997; Nestler and Aghajanian, 1997; Shippenberg *et al.*, 2009).

Research on the treatment of opioid dependence and protracted abstinence syndrome (PAS) is plentiful. However, most focus on pharmacology and medicine. The complexity of PAS and co-morbid psychiatric disorders among opioid-dependent populations make choosing an appropriate treatment difficult. Common pharmacological treatments consist of three classes: opioid antagonists (naloxone and naltrexone), opioid agonists (methadone, levomethadyl acetate and buprenorphine) and non-opioid medications (clonidine and lofexidine) (Veilleux *et al.*, 2010). Beyond the physical symptoms, methods of treatment that can improve mood are also widely used for PAS because of the severe psychological problems encountered over the course of withdrawal. The focus of these treatments is to reduce the chance of relapse and improve the physical and psychological health of patients (Nunes *et al.*, 2006; Ward *et al.*, 1999).

Many studies highlight exercise's physical and psychological benefits (Penedo and Dahn, 2005; Bize *et al.*, 2007; Packer *et al.*, 2010) and some even propose exercise as an adjunct treatment for smoking cessation, alcoholism and substance abuse (Ussher *et al.*, 2004; Weinstock *et al.*, 2008; Bock *et al.*, 2010). Tai Chi, a traditional chinese martial art that provides comprehensive physical and mental practices, is well-known for its graceful movement and mild intensity, as well as its proven beneficial effects on cardiovascular and respiratory function, immune system, hypertension, diabetes, stress and anxiety (Brown *et al.*, 1989; Wang *et al.*, 2004, 2010; Yeh *et al.*, 2006; Zhang and Fu, 2008; Jahnke *et al.*, 2010). Most recently, Tai Chi has been found to improve balance in patients with mild-to-moderate Parkinson's disease, with additional benefits of improved functional capacity and reduced falls (Li *et al.*, 2012). Based on these findings, we hypothesized that Tai Chi training might ameliorate PAS in heroin-addicted subjects during withdrawal. To measure if Tai Chi had a pronounced effect on PAS, we designed our study around using comprehensive physical parameters, the Hamilton Rating Scale for Depression (HRSD) and the rating scale of heroin withdrawal.

Methods

Subjects

We recruited 70 women with a mean age of 30.7 ± 6.3 years from the Kunming Rehabilitation Center on Drug Dependence in Yunnan, China. All participants were chosen with the following criteria: (1) they must be older than 18 years; (2) they must have a diagnosis of opioid dependence; and (3) they must have no serious disease. Thirty-seven of these participants who were physically inspected an insufficient number of times or who left the program during the period of our study were not included in the final analyses. The remaining 33 withdrawal patients we analyzed were between 18 and 41 years old, with an average age of 29.97 ± 6.74 years and an average age at first use of substance of 21.25 ± 5.06 years. As a baseline, 18 healthy women with a mean age of 26.67 ± 4.04 years (volunteers from the Kunming Institute of Zoology) were placed into a normal (N) group. The purposes, constraints, potential benefits and risks involved in the study were explained to all subjects. Informed consent forms were willingly signed by all subjects prior to study and the institutional review board of the Kunming Institute of Zoology approved this study.

Procedures

The 70 withdrawal patients were randomly assigned to either the Tai Chi (TC) group ($n = 36$) or control (C) group ($n = 34$). Every two days for six months, the TC group performed a routine consisting of a 10 min of warm-up, 1 h of Tai Chi supervised by a professional coach, and 10 min of cool-down exercises. The C group had similar levels of exercise (excluding Tai Chi) and shared the same life conditions of the TC group during the test. All assessments were conducted in the same way as the TC group. In total, 17 women in the TC group and 16 women in the C group completed the six-month trial study and were each measured three times to verify their physical condition over the course of treatment (Fig. 1).

Measurements of Physiological Parameters

Blood samples were collected from both groups under standardized conditions: in the morning before breakfast, in a seated position, and after at least 15 minutes of rest. Immune system function, complete blood count, hepatic function and renal function were measured by a commercial company (King Med Diagnostics Company, Guangzhou, China) prior to and every three months during the Tai Chi training. Subpopulations of CD3, CD4 and CD8 T lymphocytes, natural killer (NK) cells, and B lymphocytes were measured as proxy of immune system function. The complete blood count included white blood count (WBC), red blood count (RBC), hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, lymphocytes and neutrophils. Blood tests were used to measure eight factors of

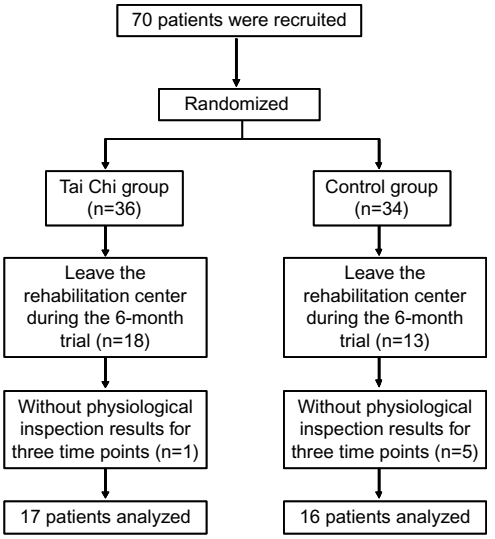

Figure 1. Flow diagram of patients enrolled in this study.

hepatic function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transferase (GGT), serum total protein (TP), albumin (A), globulin (G), albumin /globulin (A/G) and alanine aminotransferase/aspartate aminotransferase (ALT/AST). Blood urea nitrogen (BUN), creatinine (Cr) and uric acid (UA) were assayed to represent the function of kidney.

Evaluations of HRSD and the Rating Scale of Heroin Withdrawal Symptoms

Under the guidance of trained physicians, the HRSD and the rating scale of heroin withdrawal symptoms were evaluated for all patients in the TC and C group (Hamilton, 1960; Liu *et al.*, 2000). All subjects were interviewed at the beginning of the study and then regularly at 30, 60, 90, 120 and 150 days. Total score evaluations of the scales were also performed using a double-blind treatment.

Statistical Analysis

The collected data were expressed as mean $\pm$ S.D. calculated using SPSS 18 (SPSS Inc, Chicago, Illinois, USA). The physical measurement data of the N group and all withdrawal patients at the beginning of the study were analyzed using unpaired Student's t test. The N, C and TC groups were compared separately by one-way ANOVA for multiple comparisons (Bonferroni-corrected ANOVA or Tamhane's T2-corrected ANOVA). Univariate analysis with repeated measures was performed to examine the time and group effect of physiological parameters between the TC group and the C group, with $p < 0.05$ being considered statistically significant.

Results

Evaluation of Baseline Between Withdrawal Subjects and Normal Group

Using Student's *t*-tests to obtain a baseline measure between all withdrawal subjects ($n = 70$) and our normal group, we found that in all inspected parameters there were significant differences in immunity function (NK cells and B lymphocytes), anemia (HGB, MCH and MCHC), hepatic function (ALT, AST, GGT, A/G, ALT/AST and G) and three factors of renal function (Table 1), suggesting a deleterious effect of drug addiction. As we applied the baseline data of withdrawal patients that completed the six-month trial ($n = 33$), the results of comparing the 33 withdrawal subjects with the N group showed that NK cells, G and UA became non-significant while other parameters remained significant, similar to the earlier comparisons using all 70 withdrawal subjects (Table 1).

Baseline Analysis Between TC Group, C Group and N Group

The demographic profile and baseline physical parameters of the withdrawal subjects who completed the study are shown in Table 2. The N group had significantly higher values of NK cells, HGB, MCH, MCHC, Cr and lower values of B lymphocytes than the TC group ($p < 0.05$) and also displayed significantly higher levels of MCHC, ALT/AST, Cr and lower levels of ALT, AST than the C group ($p < 0.05$). We observed no statistical difference for $CD4^+$ T-cell and CD4/CD8 ratio between the TC group and the C group at the baseline ($p > 0.05$), although the TC group had a slightly higher percentage of $CD4^+$ T-cells (38.41 ± 8.00) and CD4/CD8 ratio (1.34 ± 0.59) than those of the C group ($CD4^+$ T-cell, 33.81 ± 9.41, CD4/CD8 ratio, 1.13 ± 0.59) and the N group ($CD4^+$ T-cell, 34.83 ± 7.77; CD4/CD8 ratio, 1.27 ± 0.59) (Table 2). This difference suggests that the two groups of withdrawal patients may have had some differences in these parameters at the beginning of the Tai Chi training.

Longitudinal Analysis Between the TC Group and the C Group

Univariate analysis with repeated measures revealed no significant difference at the end of six months for any group or group-by-time effects between the TC and the C group (Table 3). However, the difference of B lymphocytes tended to be significant between the TC group and the C group over the course of Tai Chi training ($p = 0.08$). The pattern of GGT tended to change significantly over time between the two groups ($p = 0.08$).

The indexes of the immune function, blood cell count, liver and kidney function of the 33 analyzed withdrawal subjects revealed remarkable changes over the six-month trial. The time effects of the six-month trial were significant for all selected indexes with the exception of RBC ($p = 0.16$), GGT ($p = 0.21$) and UA ($p = 0.06$). Both the TC group and the C group produced a similar change pattern for most of the measurements (Fig. 2).

Table 1. Baseline Comparison between the Normal Group and Withdrawal Subjects

	Normal Group ($n = 18$)	Withdrawal Subjects Enrolled ($n = 70$)	p Value[a]	Withdrawal Subjects Analyzed ($n = 33$)	p Value[b]
Immune Function					
CD3 (%)	73.33 (4.96)	76.31 (8.11)	0.056	74.67 (7.95)	0.522
CD4 (%)	34.83 (7.77)	35.07 (9.99)	0.925	36.18 (8.89)	0.591
CD8 (%)	31.22 (9.31)	36.24 (13.78)	0.148	34.09 (11.35)	0.364
CD4/CD8	1.27 (0.59)	1.17 (0.60)	0.550	1.24 (0.59)	0.880
NK (%)	15.94 (4.99)	10.74 (6.47)	0.002**	11.90 (7.70)	0.051
B (%)	9.06 (3.30)	12.03 (5.16)	0.005**	12.48 (4.80)	0.010**
Complete Blood Count					
RBC (10^{12}/L)	4.60 (0.36)	4.56 (0.44)	0.756	4.59 (0.51)	0.924
HGB (g/L)	144.94 (10.84)	135.71 (13.07)	0.007**	137.00 (12.27)	0.026*
MCV (fL)	92.00 (4.46)	89.07 (6.69)	0.083	89.58 (5.83)	0.131
MCH (pg)	31.58 (1.82)	29.87 (2.78)	0.015*	30.04 (2.34)	0.019**
MCHC (g/L)	343.56 (6.13)	335.06 (11.12)	0.002**	335.21 (8.18)	0.001**
WBC (10^9/L)	6.92 (1.36)	6.41 (1.63)	0.233	6.56 (1.98)	0.501
LYM (10^9/L)	2.39 (0.56)	2.26 (0.54)	0.350	2.13 (0.52)	0.104
NEU (10^9/L)	3.89 (1.07)	3.69 (1.34)	0.573	3.97 (1.65)	0.851
PLT (10^9/L)	197.38 (54.23)	197.44 (56.66)	0.997	195.76 (55.00)	0.919
Hepatic Function					
ALT (U/L)	14.11 (5.58)	39.46 (49.91)	0.001**	36.42 (39.15)	0.003**
AST (U/L)	18.39 (4.03)	34.76 (35.22)	0.001**	33.76 (29.34)	0.006**
GGT (U/L)	12.89 (5.60)	33.56 (36.49)	0.001**	34.15 (36.65)	0.002**
TP (g/L)	77.73 (4.55)	79.99 (5.30)	0.101	79.52 (5.40)	0.239
A (g/L)	46.42 (2.18)	46.14 (3.23)	0.727	46.21 (3.54)	0.815
G (g/L)	31.31 (2.98)	33.85 (4.46)	0.024*	33.31 (4.38)	0.089
A/G	1.49 (0.13)	1.38 (0.19)	0.033**	1.41 (0.18)	0.096
ALT/AST	1.44 (0.46)	1.09 (0.38)	0.001**	1.17 (0.45)	0.045*
Renal Function					
BUN (mmol/L)	4.38 (1.24)	3.44 (0.88)	0.006**	3.57 (1.02)	0.015**
Cr (μmol/L)	60.50 (6.86)	52.26 (6.72)	0.001**	51.85 (7.28)	0.001**
UA (μmol/L)	280.94 (59.00)	246.77 (56.00)	0.025*	251.58 (65.66)	0.120

Note: All values are presented as mean (SD). CD3: CD3+T lymphocytes; CD4: subpopulations of CD3+CD4+T lymphocytes; CD8: subpopulations of CD3+CD8+T lymphocytes; NK: natural killer cells; B:B lymphocytes; RBC: red blood count; HGB: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood count; PLT: platelets; LYM: lymphocytes; NEU: neutrophils; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; TP: serum total protein; A: albumin; G: globulin; BUN: blood urea nitrogen; Cr: creatinine; UA: uric acid. *$p < 0.05$, **$p < 0.01$. [a]p value for the comparison between healthy individuals (normal group) and all withdrawal patients enrolled in this study. [b]p value for the comparison between healthy individuals (normal group) and withdrawal patients who completed the six-month trial.

Table 2. Baseline Comparison of the Normal Individuals and Analyzed Patients with and without Tai Chi Training

	Normal Group ($n = 18$)	Control Group ($n = 16$)	Tai Chi Group ($n = 17$)
Demographic Profile			
Age (years)	26.67 (4.04)	29.60 (6.05)	30.29 (7.47)
Age at first addiction (years)	—	21.40 (6.10)	21.11 (4.12)
Time of addiction (years)	—	6.69 (5.66)	6.16 (4.98)
Immune Function			
CD3 (%)	73.33 (4.96)	74.50 (9.67)	74.82 (6.22)
CD4 (%)	34.83 (7.77)	33.81 (9.41)	38.41 (8.00)
CD8 (%)	31.22 (9.31)	35.50 (12.36)	32.76 (10.50)
CD4/CD8	1.27 (0.59)	1.13 (0.59)	1.34 (0.59)
NK (%)	15.94 (4.99)	13.56 (9.68)	10.35 (5.06)[a]
B (%)	9.06 (3.30)	11.06 (5.03)	13.82 (4.29)[a]
Complete Blood Count			
RBC (10^{12}/L)	4.60 (0.36)	4.60 (0.46)	4.58 (0.58)
HGB (g/L)	144.94 (10.84)	139.44 (14.72)	134.71 (9.30)[a]
MCV (fL)	92.00 (4.46)	90.25 (4.36)	88.94 (7.01)
MCH (pg)	31.58 (1.82)	30.37 (1.82)	29.73 (2.76)[a]
MCHC (g/L)	343.56 (6.13)	336.63 (8.47)[a]	333.88 (7.90)[a]
WBC (10^9/L)	6.92 (1.36)	6.63 (1.78)	6.49 (2.21)
LYM (10^9/L)	2.39 (0.56)	1.97 (0.51)	2.29 (0.50)
NEU (10^9/L)	3.89 (1.07)	4.19 (1.43)	3.75 (1.86)
PLT (10^9/L)	197.38 (54.23)	199.13 (60.09)	192.59 (51.41)
Hepatic Function			
ALT (U/L)	14.11 (5.58)	40.69 (37.05)[a]	32.41 (41.75)
AST (U/L)	18.39 (4.03)	33.81 (20.03)[a]	33.71 (36.68)
GGT (U/L)	12.89 (5.60)	35.00 (37.48)	33.35 (37.00)
TP (g/L)	77.73 (4.55)	80.24 (5.52)	78.84 (5.37)
A (g/L)	46.42 (2.18)	47.03 (3.39)	45.43 (3.60)
G (g/L)	31.31 (2.98)	33.21 (3.45)	33.41 (5.21)
A/G	1.49 (0.13)	1.42 (0.16)	1.39 (0.21)
ALT/AST	1.44 (0.46)	1.05 (0.45)[a]	1.28 (0.43)
Renal Function			
BUN (mmol/L)	4.38 (1.24)	3.58 (1.24)	3.56 (.79)
Cr (μmol/L)	60.50 (6.86)	49.44 (7.85)[a]	54.12 (6.08)[a]
UA (μmol/L)	280.94 (59.00)	254.31 (82.40)	249.00 (47.34)

Note: All values are presented as mean (SD). Patients in the control group and Tai Chi group completed the six-month trial, and those who did not finish the entire trial were excluded from the analysis. CD3: CD3+T lymphocytes; CD4: subpopulations of CD3+CD4+T lymphocytes; CD8: subpopulations of CD3+CD8+T lymphocytes; NK: natural killer cells; B:B lymphocytes; RBC: red blood count; HGB: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood count; PLT: platelets; LYM: lymphocytes; NEU: neutrophils; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; TP: serum total protein; A: albumin; G: globulin; BUN: blood urea nitrogen; Cr: creatinine; UA: uric acid. [a]$p < 0.05$, control group versus normal group or Tai Chi group versus normal group. There was no statistical difference for each parameter between the control group and the Tai Chi group.

Table 3. Results of Univariate Analysis with Repeated Measures

Parameter	Tai Chi Group ($n = 17$)			Control Group ($n = 16$)			*P*-Value Using Univariate Analysis with Repeated Measures		
	0 Month	3 Months	6 Months	0 Month	3 Months	6 Months	Group	Time	Group × Time
Immune Function									
CD3 (%)	74.82 (6.22)	77.47 (6.16)	74.65 (6.22)	74.50 (9.67)	79.31 (7.54)	75.13 (10.44)	0.80	0.001**	0.14
CD4 (%)	38.41 (8.00)	42.41 (8.56)	38.94 (8.80)	33.81 (9.41)	38.13 (8.37)	35.56 (9.76)	0.19	0.001**	0.83
CD8 (%)	32.76 (10.50)	30.94 (10.89)	31.65 (11.31)	35.50 (12.36)	34.13 (12.33)	34.31 (13.94)	0.49	0.02*	0.81
NK (%)	10.35 (5.06)	10.94 (5.86)	12.76 (6.40)	13.56 (9.68)	11.81 (6.76)	14.88 (10.72)	0.42	0.02**	0.28
B (%)	13.82 (4.29)	10.59 (4.15)	11.76 (4.05)	11.06 (5.03)	8.25 (4.30)	9.31 (5.07)	0.08	0.001**	0.95
Complete Blood Count									
RBC (10^{12}/L)	4.58 (0.58)	4.61 (0.58)	4.65 (0.64)	4.60 (0.46)	4.65 (0.44)	4.78 (0.39)	0.72	0.16	0.70
HGB (g/L)	134.71 (9.30)	137.53 (10.25)	150.76 (12.72)	139.44 (14.72)	138.69 (10.88)	154.88 (11.55)	0.34	0.001**	0.54
MCV (fL)	88.94 (7.01)	85.94 (7.39)	93.71 (6.05)	90.25 (4.36)	85.94 (3.47)	95.06 (3.43)	0.62	0.001**	0.35
MCH (pg)	29.73 (2.76)	30.12 (3.07)	31.59 (2.74)	30.37 (1.82)	29.89 (1.46)	31.96 (1.06)	0.73	0.001**	0.20
WBC (10^9/L)	6.49 (2.21)	5.29 (1.37)	6.80 (2.52)	6.63 (1.78)	5.88 (1.19)	6.87 (1.99)	0.66	0.001**	0.44
LYM (10^9/L)	2.29 (0.50)	1.72 (0.36)	2.01 (0.52)	1.97 (0.51)	1.74 (0.48)	1.93 (0.61)	0.39	0.001**	0.11
NEU (10^9/L)	3.75 (1.86)	3.16 (1.03)	4.21 (1.95)	4.19 (1.43)	3.74 (0.96)	4.42 (1.65)	0.39	0.001**	0.68
PLT (10^9/L)	192.59 (51.41)	148.59 (51.41)	212.06 (61.09)	199.13 (60.09)	144.75 (40.92)	199.00 (38.26)	0.84	0.001**	0.28

Table 3. (*Continued*)

Parameter	Tai Chi Group ($n = 17$)			Control Group ($n = 16$)			*P*-Value Using Univariate Analysis with Repeated Measures		
	0 Month	3 Months	6 Months	0 Month	3 Months	6 Months	Group	Time	Group × Time
Hepatic Function									
ALT (U/L)	32.41 (41.75)	42.06 (34.71)	67.47 (88.30)	40.69 (37.05)	66.88 (63.52)	55.38 (39.33)	0.68	0.001**	0.16
AST(U/L)	33.71 (36.68)	40.82 (33.58)	55.76 (58.76)	33.81 (20.03)	46.38 (31.08)	42.50 (25.07)	0.83	0.001**	0.12
GGT (U/L)	33.35 (37.00)	27.76 (26.45)	45.82 (48.62)	35.00 (37.48)	32.75 (25.91)	31.69 (27.63)	0.87	0.21	0.08
TP (g/L)	78.84 (5.37)	81.41 (14.93)	84.91 (11.49)	80.24 (5.52)	86.00 (3.96)	87.68 (7.89)	0.24	0.001**	0.77
A (g/L)	45.43 (3.60)	50.92 (9.51)	50.16 (9.93)	47.03 (3.39)	49.39 (2.19)	48.49 (2.33)	0.61	0.001**	0.61
G (g/L)	33.41 (5.21)	37.01 (6.08)	39.46 (7.93)	33.21 (3.45)	36.61 (4.03)	39.18 (7.94)	0.80	0.001**	0.92
Renal Function									
BUN (mmol/L)	3.56 (0.79)	3.75 (0.82)	4.34 (1.08)	3.58 (1.24)	4.11 (0.82)	4.15 (0.81)	0.81	0.001**	0.29
Cr (μmol/L)	54.12 (6.08)	56.44 (15.14)	53.52 (14.54)	49.44 (7.85)	56.75 (6.14)	53.50 (6.03)	0.94	0.001**	0.66
UA (μmol/L)	249.00 (47.34)	251.12 (66.49)	260.41 (57.42)	254.31 (82.40)	279.31 (86.33)	276.19 (84.63)	0.49	0.06	0.34

Note: All values are presented as mean (SD). CD3: CD3+T lymphocytes; CD4: subpopulations of CD3+CD4+T lymphocytes; CD8: subpopulations of CD3+CD8+T lymphocytes; NK: natural killer cells; B:B lymphocytes; RBC: red blood count; HGB: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood count; PLT: platelets; LYM: lymphocytes; NEU: neutrophils; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; TP: serum total protein; A: albumin; G: globulin; BUN: blood urea nitrogen; Cr: creatinine; UA: uric acid. $^{*}p < 0.05$, $^{**}p < 0.01$.

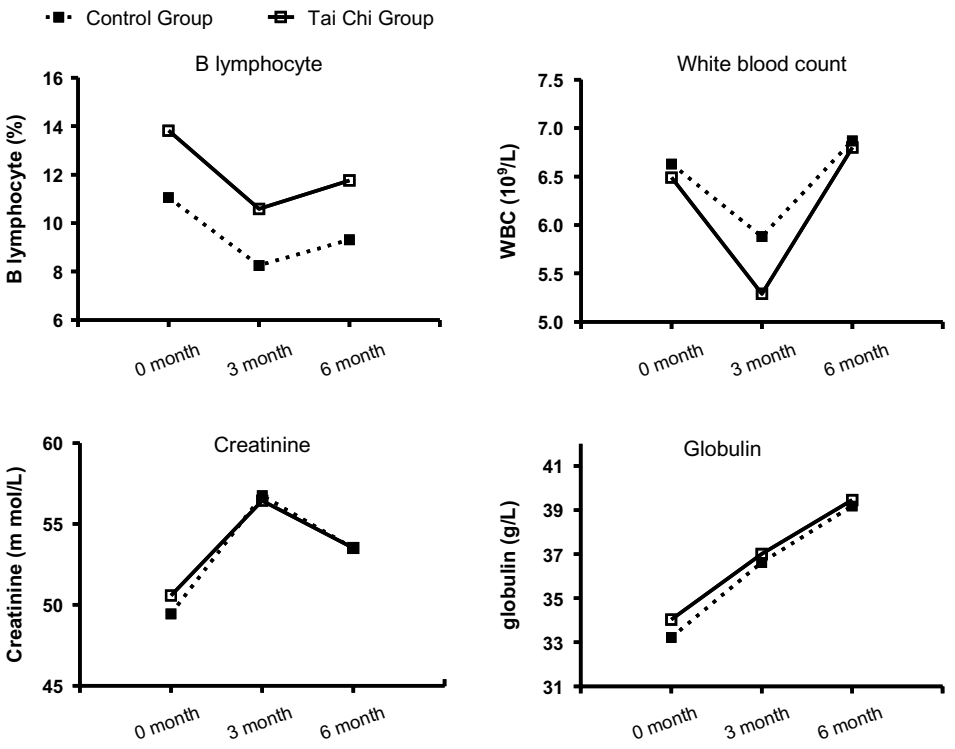

Figure 2. Changing pattern of representative physical parameters of different measurements at zero, three and six months.

Scores of HRSD and Rating Scale of Heroin Withdrawal Syndromes

Questionnaires of the HRSD and rating scale of heroin withdrawal syndromes were administered at the beginning of the study and then at monthly intervals for five months during the double-blind study. The total score differences of HRSD and rating scale of heroin withdrawal syndromes between the TC group and the C group were statistically different only at 60 days ($p < 0.05$) and during no other times (Table 4). We obtained the trends of total score variation during the study time, and the diagram of both groups along trend down. The trends for the C group, however, varied substantially from those of the TC group. Graphs of the scores of the HRSD and rating scale of heroin withdrawal syndromes illustrated strong fluctuation in the C group, particularly around the 60-day mark, while the diagram of TC group decreases smoothly for the duration of the study (Fig. 3).

Discussion

Tai Chi has been noted to confer potential psychological and physiological benefits to participants, as well as considerably improve cardiovascular and respiratory function, metabolic control, immune system function and psychological dysfunction, and it is

Table 4. Total Scores of the HRSD and the Rating Scale of Heroin Withdrawal Symptoms of Patients with and without Tai Chi Treatment

Total Score	Control Group ($n = 16$)	Tai Chi Group ($n = 17$)	p Value
Rating scale of heroin withdrawal symptoms			
0 day	14.07 (14.24)	8.65 (8.70)	0.198
30 days	11.62 (8.36)	8.06 (5.89)	0.182
60 days	17.13 (13.96)	8.18 (7.67)	0.029*
90 days	8.25 (6.66)	6.71 (6.10)	0.492
120 days	7.80 (6.07)	4.21 (4.23)	0.101
150 days	5.09 (4.04)	4.12 (3.90)	0.530
HRSD			
0 day	10.13 (9.29)	7.76 (6.29)	0.400
30 days	6.85 (5.73)	5.88 (4.47)	0.608
60 days	10.13 (8.72)	4.59 (6.77)	0.049*
90 days	6.73 (5.47)	4.53 (6.92)	0.330
120 days	3.80 (3.52)	3.15 (4.52)	0.713
150 days	4.09 (3.94)	2.53 (2.98)	0.243

Note: Values are presented as mean (SD). $^{*}p < 0.05$.

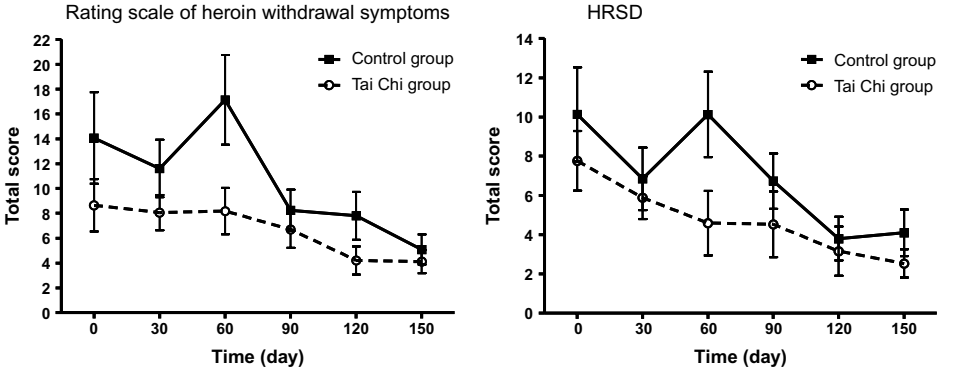

Figure 3. Changing pattern for total scores of HRSD and rating scale of heroin withdrawal symptoms over the course of the trial for the Tai Chi group (circles) and the control group (squares). Values shown are means of patient scores in each group and error bars are standard error of scores.

likewise regarded as a particularly helpful exercise regimen for the elderly (Rogers *et al.*, 2009; Maciaszek and Osinski, 2010; Romero Zurita, 2010; Guan and Koceja, 2011). To our knowledge, our study is the first to investigate the effects of Tai Chi as a complementary treatment method for PAS. We chose to measure numerous parameters that reportedly have a close relationship with drug addiction and withdrawal symptoms, including immune system function, complete blood count, hepatic function, and renal

function, in order to find basal markers that reflect the effects of Tai Chi on the health of recovering drug addicts suffering from withdrawal.

Former studies on PAS focused on the function of central nervous system and the opioid usage's damage to the immune system (McCarthy *et al.*, 2001). Most addictive drugs inhibit the growth and division of cells, inducing cell apoptosis. This inhibitory effect occurs throughout the body and can impair the organs, especially those involved in the metabolism of drugs, such as the liver and kidney (Nestler and Aghajanian, 1997). The compared parameters between the N group and all withdrawal subjects showed significant differences in NK cells, B lymphocytes subpopulation, HGB, MCH, MCHC, ALT, AST, GGT, G, A/G, ALT/AST, BUN, Cr and UA ($p < 0.05$). These results reflected that all the physical functions we inspected on immunity function, anemia, hepatic function and renal function were different between normal and withdrawal individuals. Reece (2007) found that serum globulins, ALT, Cr, BUN were significantly higher in the drug addicted group compared to the normal group, while Gordon (1978) reported a low BUN and high UA level in patients with acute opiate PAS. Our results are not fully consistent with these earlier observations, as we found that the levels of UA, Cr and BUN were all lower in withdrawal subjects than in healthy individuals, though the exact reason for this discrepancy is unknown. Note that the parameters that represent hepatic function (ALT, AST and GGT) were at least two-fold higher in withdrawal subjects than in healthy individuals.

A proportion of all withdrawal subjects in both the C group and the TC group completed the trial. All of the parameters of the group and group-by-time effects showed no significant difference, and the change pattern was similar between the TC group and the C group at the end of six months. The values of physical parameters regarding renal function increased to nearly reach the levels of healthy individuals after the trial; these results imply that renal function improved in withdrawal subjects, though the effect of Tai Chi was not obvious. Similarly, the levels of hepatic function parameters increased after six months in all withdrawal subjects irrespective of Tai Chi training, suggesting that all drug-addicted patients may experience chronic hepatic damage, including a high detoxification burden and/or viral infections.

Habitual drug abuse will lead to chronic antigenic overload, immune hyperstimulation and immunosuppression (Eisenstein and Hilburger, 1998; Vallejo *et al.*, 2004). Previous findings indicated various immune-competent cells express opioid receptors, and long-time administration of opioids induces chronic inflammation and cell apoptosis through activation of phagocytic activity and antibody responses (McCarthy *et al.*, 2001). Our results showed that the percentage of NK cells increased from 10.35 ± 5.06 to 12.76 ± 6.40 and the percentage of B lymphocytes decreased from 13.82 ± 4.29 to 11.76 ± 4.05 in the TC group over the course of the six-month training. A similar pattern was observed in the C group: the percentage of NK cells increased from 13.56 ± 9.68 to 14.88 ± 10.72 and the percentage of B lymphocytes decreased from 11.06 ± 5.03 to 9.31 ± 5.07. Although the percentages of NK and B cells did not reach the levels of the N group during the trial, our current observations suggest that the immune system has been reinforced in the critical PAS period (Table 3).

The time effects of the six-month trial showed that all withdrawal subjects had a significant difference in immunity function, anemia, hepatic function and renal function except for RBC ($p = 0.16$), GGT ($p = 0.21$) and UA ($p = 0.06$). Withdrawal of opioids, however, precipitates a characteristic syndrome of signs and symptoms, indicating significant disturbance of many body functions. After a few difficult days, the recovery process becomes evident. After six to nine months or longer, patients appear to have recovered physically (Himmelsbach, 1942). In this situation, the parameters we chose may undergo extreme changes that are nonetheless not strong or indicative enough to determine the outcome of using Tai Chi as part of treatment among patients suffering withdrawal. Subsequently, increasing the trial time to one or two years may provide more interesting and conclusive findings.

Beyond the physical symptoms, drug dependence is associated with co-morbid psychopathology, which can persist following abstinence (Kalechstein *et al.*, 2002). Gawin and Kleber (1986) suggested that the presence of depressive symptoms, such as dysphoria, anhedonia, anergia and irritability, can occur for variable periods of time following last usage of cocaine. Aside from measuring the physical effects of Tai Chi, the second aim of our study was to evaluate Tai Chi's effects on the improvement of PAS in recovering drug users suffering withdrawal. Our study showed the total score of HRSD and rating scale of heroin withdrawal symptoms among the TC group was not better much than C group, except at the 60-day interval; however, the trend of the diagram for the TC group showed small fluctuation compared to the C group. Taking these results together, this suggests some positive effects of Tai Chi on the improvement of PAS in patients going through withdrawal.

Though several of our measurements were inconclusive, the collected data suggests future studies can expand the sample size and prolong the length of the trial time to achieve more conclusive results, though such trails are difficult and costly, especially in human terms. Future studies can further shed light on the role of exercise in general, and Tai Chi in particular, by examining dopamine (DA), serotonin (5-HT) (Nestler and Aghajanian, 1997; Schmidt *et al.*, 1997), melatonin (Zhdanova and Piotrovskaya, 2000; Peles *et al.*, 2007), β-endorphins (β-EP) (Emrich *et al.*, 1983), estrogen (Carroll *et al.*, 2004) and Pittsburgh Sleep Quality Index (PSQI) (Buysse *et al.*, 1989; Stein *et al.*, 2004), all of which may be more sensitive and more specific indicators in evaluating the improvements of physical health in recovering drug users suffering from withdrawal.

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References

Bize, R., J.A. Johnson and R.C. Plotnikoff. Physical activity level and health-related quality of life in the general adult population: a systematic review. *Prev. Med.* 45: 401–415, 2007.

Bock, B.C., K.M. Morrow, B.M. Becker, D.M. Williams, G. Tremont, R.B. Gaskins, E. Jennings, J. Fava and B.H. Marcus. Yoga as a complementary treatment for smoking cessation: rationale, study design and participant characteristics of the Quitting-in-Balance study. *BMC Complement. Altern. Med.* 10: 14, 2010.

Brown, D.D., W.G. Mucci, R.K. Hetzler and R.G. Knowlton. Cardiovascular and ventilatory responses during formalized Tai Chi Chuan exercise. *Res. Q. Exerc. Sport* 60: 246–250, 1989.

Buysse, D.J., C.F. Reynolds, 3rd, T.H. Monk, S.R. Berman and D.J. Kupfer. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28: 193–213, 1989.

Carroll, M.E., W.J. Lynch, M.E. Roth, A.D. Morgan and K.P. Cosgrove. Sex and estrogen influence drug abuse. *Trends Pharmacol. Sci.* 25: 273–279, 2004.

Eisenstein, T.K. and M.E. Hilburger. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J. Neuroimmunol.* 83: 36–44, 1998.

Emrich, H.M., L. Nusselt, C. Gramsch and S. John. Heroin addiction: beta-endorphin immunoreactivity in plasma increases during withdrawal. *Pharmacopsychiatria* 16: 93–96, 1983.

Gawin, F.H. and H.D. Kleber. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. *Arch. Gen. Psychiatry* 43: 107–113, 1986.

Gordon, D. Hematologic abnormalities and pain during acute opiate abstinence syndrome. *Clin. Toxicol.* 12: 563–578, 1978.

Guan, H. and D.M. Koceja. Effects of long-term Tai Chi practice on balance and H-reflex characteristics. *Am. J. Chin. Med.* 39: 251–260, 2011.

Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23: 56–62, 1960.

Himmelsbach, C.K. Clinical studies of drug addiction — physical dependence, withdrawal and recovery. *Arch. Intern. Med.* 69: 766–772, 1942.

Jahnke, R., L. Larkey, C. Rogers, J. Etnier and F. Lin. A comprehensive review of health benefits of qigong and Tai Chi. *Am. J. Health Promot.* 24: e1–e25, 2010.

Kalechstein, A.D., T.F. Newton and A.H. Leavengood. Apathy syndrome in cocaine dependence. *Psychiatry Res.* 109: 97–100, 2002.

Leshner, A.I. Addiction is a brain disease, and it matters. *Science* 278: 45–47, 1997.

Li, F., P. Harmer, K. Fitzgerald, E. Eckstrom, R. Stock, J. Galver, G. Maddalozzo and S.S. Batya. Tai Chi and postural stability in patients with Parkinson's disease. *N. Engl. J. Med.* 366: 511–519, 2012.

Liu, C., G.Z. Xu and J.W. Zheng. Revision of rating scale for protracted withdrawal symptoms of heroin addicts. *Chin. J. Drug Depend.* 9: 132–135, 2000.

Maciaszek, J. and W. Osinski. The effects of Tai Chi on body balance in elderly people — a review of studies from the early 21st century. *Am. J. Chin. Med.* 38: 219–229, 2010.

McCarthy, L., M. Wetzel, J.K. Sliker, T.K. Eisenstein and T.J. Rogers. Opioids, opioid receptors and the immune response. *Drug Alcohol Depend.* 62: 111–123, 2001.

Nestler, E.J. and G.K. Aghajanian. Molecular and cellular basis of addiction. *Science* 278: 58–63, 1997.

Nunes, E.V., J.L. Rothenberg, M.A. Sullivan, K.M. Carpenter and H.D. Kleber. Behavioral therapy to augment oral naltrexone for opioid dependence: a ceiling on effectiveness? *Am. J. Drug Alcohol Abuse* 32: 503–517, 2006.

Packer, N., L. Hoffman-Goetz and G. Ward. Does physical activity affect quality of life, disease symptoms and immune measures in patients with inflammatory bowel disease? A systematic review. *J. Sports Med. Phys. Fitness* 50: 1–18, 2010.

Peles, E., T. Hetzroni, R. Bar-Hamburger, M. Adelson and S. Schreiber. Melatonin for perceived sleep disturbances associated with benzodiazepine withdrawal among patients in methadone maintenance treatment: a double-blind randomized clinical trial. *Addiction* 102: 1947–1953, 2007.

Penedo, F.J. and J.R. Dahn. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Curr. Opin. Psychiatry* 18: 189–193, 2005.

Reece, A.S. Evidence of accelerated ageing in clinical drug addiction from immune, hepatic and metabolic biomarkers. *Immun. Ageing* 4: 6, 2007.

Rogers, C.E., L.K. Larkey and C. Keller. A review of clinical trials of Tai Chi and qigong in older adults. *West J. Nurs. Res.* 31: 245–279, 2009.

Romero Zurita, A. Effects of Tai Chi on health-related quality of life in the elderly. *Rev. Esp. Geriatr. Gerontol.* 45: 97–102, 2010.

Schmidt, L.G., P. Dufeu, A. Heinz, S. Kuhn and H. Rommelspacher. Serotonergic dysfunction in addiction: effects of alcohol, cigarette smoking and heroin on platelet 5-HT content. *Psychiatry Res.* 72: 177–185, 1997.

Shippenberg, T.S., V.I. Chefer and A.C. Thompson. Delta-opioid receptor antagonists prevent sensitization to the conditioned rewarding effects of morphine. *Biol. Psychiatry* 65: 169–174, 2009.

Stein, M.D., D.S. Herman, S. Bishop, J.A. Lassor, M. Weinstock, J. Anthony and B.J. Anderson. Sleep disturbances among methadone maintained patients. *J. Subst. Abuse Treat.* 26: 175–180, 2004.

Ussher, M., A.K. Sampuran, R. Doshi, R. West and D.C. Drummond. Acute effect of a brief bout of exercise on alcohol urges. *Addiction* 99: 1542–1547, 2004.

Vallejo, R., O. de Leon-Casasola and R. Benyamin. Opioid therapy and immunosuppression: a review. *Am. J. Ther.* 11: 354–365, 2004.

Veilleux, J.C., P.J. Colvin, J. Anderson, C. York and A.J. Heinz. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. *Clin. Psychol. Rev.* 30: 155–166, 2010.

Wang, C., R. Bannuru, J. Ramel, B. Kupelnick, T. Scott and C.H. Schmid. Tai Chi on psychological well-being: systematic review and meta-analysis. *BMC Complement. Altern. Med.* 10: 23, 2010.

Wang, C., J.P. Collet and J. Lau. The effect of Tai Chi on health outcomes in patients with chronic conditions: a systematic review. *Arch. Intern. Med.* 164: 493–501, 2004.

Ward, J., W. Hall and R.P. Mattick. Role of maintenance treatment in opioid dependence. *Lancet* 353: 221–226, 1999.

Weinstock, J., D. Barry and N.M. Petry. Exercise-related activities are associated with positive outcome in contingency management treatment for substance use disorders. *Addict. Behav.* 33: 1072–1075, 2008.

Yeh, S.H., H. Chuang, L.W. Lin, C.Y. Hsiao and H.L. Eng. Regular Tai Chi chuan exercise enhances functional mobility and CD4CD25 regulatory T cells. *Br. J. Sports Med.* 40: 239–243, 2006.

Zhang, Y. and F.H. Fu. Effects of 14-week Tai Ji Quan exercise on metabolic control in women with type 2 diabetes. *Am. J. Chin. Med.* 36: 647–654, 2008.

Zhdanova, I.V. and V.R. Piotrovskaya. Melatonin treatment attenuates symptoms of acute nicotine withdrawal in humans. *Pharmacol. Biochem. Behav.* 67: 131–135, 2000.