

## ORIGINAL RESEARCH

# Treating erectile dysfunction with sildenafil alone versus combined with vitamin D<sub>3</sub> in patients with low serum 25-hydroxy vitamin D<sub>3</sub>: a prospective randomized controlled open trial

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**Abstract**

This study aimed to compare the efficacy and risk of adverse events of sildenafil plus vitamin D<sub>3</sub> versus sildenafil alone in improving erectile dysfunction (ED) in ED patients with low serum 25-hydroxy vitamin D<sub>3</sub> (25-(OH)D<sub>3</sub>). The clinical data of ED patients with low serum 25-(OH)D<sub>3</sub> treated at our center from December 2015 to December 2020 were retrieved, and the patients (n = 157) were randomly divided into an experimental group (n = 80) or a control group (n = 77). The experimental group was treated with 1 capsule of vitamin D<sub>3</sub> (400u) daily for a month and advised to use 100 mg sildenafil (po) within 1 hour before sexual intercourse, while the control group was only given 100 mg sildenafil (po) 1 hour before sexual intercourse. The indexes of international erectile function (IIEF-5), serum 25-(OH)D<sub>3</sub> level, testosterone (T) level and adverse events between the two groups were compared before and after treatment. The results showed that the IIEF-5 values of the two groups were significantly higher after treatment than before treatment ( $p < 0.05$ ). However, the serum levels of 25-(OH)D<sub>3</sub> and T in the experimental group were significantly higher than before treatment ( $p < 0.05$ ), while no significant differences were observed in the same markers in the control group before and after treatment ( $p > 0.05$ ). The overall effective rate, serum 25-(OH)D<sub>3</sub> level and T level in the experimental group were significantly higher than the control group ( $p < 0.05$ ). During the treatment, no significant difference in adverse events was observed between the two groups ( $p > 0.05$ ), which mostly comprised mild and tolerable headache, dyspepsia, back pain and muscle soreness, not requiring any medical intervention. Although both methods could effectively treat ED patients with low 25-(OH)D<sub>3</sub>, the efficacy of sildenafil plus vitamin D<sub>3</sub> was significantly superior to sildenafil alone, and the adverse reactions are mild and tolerable, which is worthy of clinical application.

**Keywords**Sildenafil; Vitamin D<sub>3</sub>; Erectile dysfunction; 25-hydroxy vitamin D<sub>3</sub>

## 1. Introduction

Erectile dysfunction (ED) refers to the inability of men to continuously obtain or maintain sufficient erectile function for satisfactory sex [1], which was reported to be associated with various risk factors such as hypertension, diabetes [2], coronary heart disease, *etc.* [3–9]. In recent years, more and more attention has been paid to the correlation between vitamin D deficiency and ED [10–13]. Many andrologists consider vitamin D testing as an important evaluation marker for ED patients. However, due to limited research in this field, the actual clinical effects of increasing vitamin D levels in improving erectile function remain unclear. Vitamin D generates 25-(OH)D<sub>3</sub> in response to liver microsomes. 25-(OH)D<sub>3</sub> is

stable in the human body, has a long half-life, and can be used as an indicator for assessing vitamin D content. Previous research showed more than 30% of ED patients had a serum 25-(OH)D<sub>3</sub> level  $< 30$  ng/mL [14]. Other studies identified a strong link between high and low testosterone (T) levels and erectile function [15]. For patients with hypogonadism with various causes, increasing T levels in the body was reported to improve erectile function [16, 17].

Sildenafil is rapidly absorbed by the body when taken orally. It has a half-life of about 3–5 hour, with an average absolute bioavailability of over 40%. Peak plasma concentration (C<sub>max</sub>) can be reached within 30 min to 120 min (median, 60 min) after fasting. After a high-fat diet, the peak time (T<sub>max</sub>) was reported to be delayed by an average of 1 hour,

and the average  $C_{max}$  decreased by nearly 30% whilst not significantly affecting the degree of absorption. The clearance of sildenafil in the human body mainly occurs in the liver. About 80% of the drugs are excreted through feces and a small amount in the urine. Presently, no studies have found any significant effect of smoking on sildenafil's pharmacokinetics, pharmacodynamics, safety, or tolerability.

Clinically, considering the lack of research in this field, whether vitamin D supplementation can effectively improve ED, especially in Chinese men, deserves further clarification. Thus, this present study aimed to compare the efficacy and adverse reactions of two treatment methods in treating ED patients with low serum 25-(OH) $D_3$ .

## 2. Materials and methods

This study was conducted on 157 ED patients with low serum 25-(OH) $D_3$  in the expert outpatient service of the Urology Department of Anqing Hospital of People's Liberation Army Navy in China from December 2015 to December 2020. Using the random number table method, all patients were divided into an experimental group ( $n = 80$ ) and a control group ( $n = 77$ ).

### 2.1 Methods

All the participants were interviewed to obtain a detailed personal and past history of medical diseases that could be a risk factor for ED, in particular diabetes mellitus, hypertension, coronary heart disease and chronic liver, kidney or neurological disorders. A history of pelvic trauma or pelvic surgery and psychedelic or psychotropic drug intake, especially those that could affect sexual function, was also investigated. The presence of factors such as anxiety, depression, phobia or a history of any psychic disorders that could precipitate psychogenic ED was also assessed.

### 2.2 Inclusion criteria

(1) All patients were aged  $\geq 35$  years, and the duration of ED was  $\geq 1$  year; (2) All patients were married or had regular sexual partner(s) and had sex  $\geq 4$  times per month; (3) The spouse or sexual partner was not satisfied with the sex life but had not yet demonstrated negative feelings of resistance, such as complaint, sexual indifference, *etc.*; (4) Had indexes of international erectile function (IIEF-5) values  $\leq 21$  and normal liver and kidney function and electrolyte levels; (5) Serum 25-(OH) $D_3$   $< 30$  ng/mL; (6) Had not received immunosuppressive agents or vitamin D drugs in the past 6 months; (7) Consented to the study and signed the informed consent form.

### 2.3 Exclusion criteria

(1) Patients with severe neurological and psychiatric diseases, psychological diseases, and abnormal hormone levels; (2) Patients with severe liver and kidney insufficiency, hypertension, coronary heart disease, diabetes mellitus and allergy to the study drugs; (3) Patients with genitourinary inflammation, abnormal libido or other sexual dysfunction diseases such as priapism; (4) Patients with genital trauma, surgical history, genital dysplasia or genital deformity; (5) Patients with a long

history of alcoholism or drug abuse; (6) Patients with a history of abnormal bone metabolism or hypercalcemia, hyperphosphatemia, and hypermagnesemia; (7) Those unresponsive to prior sildenafil treatment.

### 2.4 Treatment method

The experimental group was given one capsule of vitamin  $D_3$  (400 U) (H35021450, Sinopharmholding Star Shark Pharmaceutical (Xiamen) Co., LTD., Xiamen, China) daily for one month and 100 mg oral sildenafil (H20020526, Pfizer Pharmaceutical Co., LTD, Dalian, China) within 1 hour before sex, while the control group was advised to take 100 mg oral sildenafil within 1 hour before sex. All patients were advised not to take other drugs and quit smoking and alcohol during the treatment. They were also advised to keep a healthy diet and avoid taking medications that could affect ED, such as antioxidants and hormones, to reduce the risks of potential interference with the study results.

### 2.5 Observation

The IIEF-5 values of the study participants were evaluated before treatment and on the last day of treatment. The serum 25-(OH) $D_3$  and T levels were compared between the two groups before and after treatment, and the adverse reactions during treatment were evaluated. The treatment effect was divided into three categories: significantly effective, valid, and invalid. Significantly effective was allocated to patients with IIEF-5 values  $< 22$  points after treatment but had increased by  $\geq 5$  points compared to before treatment. Comparatively, patients with IIEF-5 values  $< 22$  points that increased by 2–4 points compared to before treatment were classified as Valid, and those with IIEF-5 values  $< 22$  points but increased by  $\leq 1$  point or even lower than before treatment were classified as Invalid. The total effective rate was obtained based on the following formula: total effective rate = significantly effective rate + valid rate.

### 2.6 Methods for testing testosterone

This study used SIEMENS Atellica IM to determine the patients' serum testosterone (T) levels, based on the following steps: 1. Add 20  $\mu$ L sample and 90  $\mu$ L auxiliary reagent to the reaction cup and incubate for 9 min at 37 °C; 2. Add 50  $\mu$ L labeling reagent and 150  $\mu$ L solid phase and incubate for 3 min at 37 °C; 3. Perform separation and suction, followed by rinsing the colorimetric cup with a cleaning solution; 4. Remove 300  $\mu$ L acid and base reagents to initiate chemiluminescence reactions; 5. Data analysis. The kit comprised a primary kit (contained a labeled reagent and a solid phase reagent), an auxiliary kit (contained a release agent), a calibrator, and a standard curve card. The main test package included a Marked test agent: 10.0 mL/box, with acridine ester labeled semi-reactive agent (36  $\mu$ g/mL), placed in buffer salt water containing anti-rot agent; a Solid-phase test agent: 17.0 mL/box, streptavidin-coated latex particles (0.33 g/L), placed in buffer brine containing anti-rot agent; and an Adjuvant package: Release agent: 10.0 mL/box, solid alcohol release agent (0.4  $\mu$ g/mL), biotin sheep monoclonal anti-testosterone antibody

(20182400442, East Walpole, MA, USA) ( $27 \mu\text{g/L}$ ) placed in buffer saline containing an antiseptic agent. Calibration was performed with 2.0 mL/vial. After resolution, low or high levels of estradiol, testosterone, cortisol, and progesterone were dissolved in human plasma of activated carbon-treated defibrinogen containing sodium azide (0.1%) and preservatives.

## 2.7 Statistical methods

The SPSS v24 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The measurement data are presented as “ $X \pm s$ ” by normal test. *T*-test was used for comparison between the two groups and before and after treatment. Enumeration data are expressed as the number of cases and percentage. The chi-square test was used for comparison between the two groups and before and after treatment in the same group. The test standard was set as  $\alpha = 0.05$ .  $p < 0.05$  was considered statistically significant.

## 3. Result

### 3.1 Related indicators of the two groups before treatment:

For the experimental group, the patient's age ranged between 41 and 58 years (mean:  $49.25 \pm 5.29$  years), the course of ED was 1–5 years (mean:  $2.98 \pm 1.96$  years), their body mass index (BMI) was 22.5–29.3  $\text{kg/m}^2$  (mean:  $27.33 \pm 1.66 \text{ kg/m}^2$ ), 25 were smokers (accounting for 61.54% of the group cases), blood glucose (GLU) was 3.95–5.98 mmol/L (mean:  $4.89 \pm 0.96$  mmol/L), total cholesterol (TC) was 2.95–5.63 mmol/L (mean:  $4.05 \pm 1.12$  mmol/L), triglyceride (TG) was 0.61–1.46 mmol/L (mean:  $1.03 \pm 0.41$  mmol/L), high-density lipoprotein cholesterol (HDL-C) was 0.95–1.93 mmol/L (mean:  $1.52 \pm 0.46$  mmol/L), non-high-density lipoprotein cholesterol (N-HDL) was 1.96–3.81 mmol/L (mean:  $2.64 \pm 1.23$  mmol/L), very low-density lipoprotein cholesterol (VLDL) was 0.25–0.53 mmol/L (mean:  $0.34 \pm 0.10$  mmol/L), low-density lipoprotein cholesterol (LDL-C) ranged from 0.05–3.01 mmol/L (mean:  $1.98 \pm 0.79$  mmol/L). The IIEF-5 values ranged from 6 to 18 (mean:  $10.03 \pm 3.01$ ). The serum 25-(OH) $\text{D}_3$  level was 13.9–24 ng/mL (mean:  $18.25 \pm 4.93$  ng/mL), and serum T level was 8.73–18.29 nmol/L (mean:  $11.42 \pm 2.76$  nmol/L).

In the control group, the patient's age was 42–56 years (mean:  $48.86 \pm 5.51$  years), the course of ED was 2–4 years (mean:  $3.06 \pm 1.87$  years), BMI was 23.5–29.8  $\text{kg/m}^2$  (mean:  $27.12 \pm 1.63 \text{ kg/m}^2$ ), 23 were smokers (accounting for 60.53% of the group cases). Their GLU was 3.91–5.86 mmol/L (mean:  $4.76 \pm 0.93$  mmol/L), TC was 2.89–5.51 mmol/L (mean:  $3.96 \pm 0.98$  mmol/L), TG was 0.88–1.53 mmol/L (mean:  $1.07 \pm 0.39$  mmol/L), HDL-C was 0.97–1.91 mmol/L (mean:  $1.48 \pm 0.41$  mmol/L), N-HDL was 2.01–3.94 mmol/L (mean:  $2.71 \pm 1.13$  mmol/L), VLDL was 0.28–0.56 mmol/L (mean:  $0.37 \pm 0.08$  mmol/L), LDL-C was 0.07–3.45 mmol/L (mean:  $2.04 \pm 0.65$  mmol/L). The IIEF-5 values ranged from 5 to 17 (mean:  $9.79 \pm 3.13$ ). The serum 25-(OH) $\text{D}_3$  level was 14.1–25.5 ng/mL (mean:  $18.61 \pm 4.87$  ng/mL), and their serum T level was 8.84–19.63 nmol/L (mean:  $11.63 \pm 2.58$  nmol/L). There

was no significant difference in general data ( $p > 0.05$ , Table 1) and clinical data ( $p > 0.05$ , Table 2) between the two groups.

## 3.2 Clinical efficacy and adverse reactions

All patients were followed up after treatment. In the experimental group, the treatment of 31 patients was significantly effective, valid for 39 patients, and invalid for 10 patients. In the control group, the treatment of 12 patients was significantly effective, valid for 41 patients, and invalid for 24 patients.

For the experimental group, the mean IIEF-5 values of the patients' were  $17.79 \pm 5.23$  points after treatment, their mean serum 25-(OH) $\text{D}_3$  level was  $45.37 \pm 5.48$  ng/mL, and their mean serum T level was  $29.41 \pm 3.63$  nmol/L. Comparatively, for the control group, the mean IIEF-5 values were  $15.05 \pm 5.17$  points after treatment, the mean serum 25-(OH) $\text{D}_3$  level was  $20.13 \pm 4.06$  ng/mL, and the mean serum T level was  $12.08 \pm 2.65$  nmol/L.

The main adverse reactions in the two groups were headache, dyspepsia, nasal congestion and dizziness [18–20]. All the participants' symptoms were mild and tolerable and required no medical intervention. The specific adverse reactions were as follows: 6 patients in the experimental group had adverse reactions during treatment, accounting for 7.50%, which comprised headache in 2 cases, dyspepsia in 1 case, and nasal congestion in 3 cases. In the control group, 4 patients had adverse reactions during the treatment, accounting for 5.19%, and comprising nasal congestion in 2 cases, dizziness in 1 case, and dyspepsia in 1 case.

## 3.3 Within-group comparison

The IIEF-5 values in the two groups after treatment were significantly improved compared with those before treatment ( $p < 0.05$ ), with a *t*-value of 8.05 for the experimental group and 5.03 for the control group. The serum levels of 25-(OH) $\text{D}_3$  and T in the experimental group after treatment were significantly increased compared with those before treatment, with a *t*-value of 9.38 and 7.84, respectively (all  $p < 0.05$ ). There were no significant differences in serum 25-(OH) $\text{D}_3$  and T levels in the control group after treatment compared with those before treatment (*t*, 1.75 and 0.39, respectively, all  $p > 0.05$ , Table 3).

## 3.4 Between-group comparison

At the end of the study, the treatment was significantly effective for 31 patients and valid for 39 patients in the experimental group, demonstrating a total effective rate of 87.50%. In the control group, the treatment was significantly effective for 12 patients and valid for 41 patients, demonstrating a total effective rate of 68.83%. The significantly effective rate and total effective rate of the experimental group were significantly higher than those of the control group ( $\chi^2 = 3.94$ ,  $p < 0.05$ ). The mean serum 25-(OH) $\text{D}_3$  level of the experimental group was  $45.37 \pm 5.48$  ng/mL, while that of the control group was  $20.13 \pm 4.06$  ng/mL, and the difference was statistically significant ( $t = 8.93$ ;  $p < 0.05$ ). The mean serum T level in the experimental group was  $29.41 \pm 3.63$  nmol/L compared with  $12.08 \pm 2.65$  nmol/L in the control group, and the difference

**TABLE 1. Comparison of the general data of the two groups.**

Baseline characteristics	Experimental group (n = 80)	Control group (n = 77)	Statistics	<i>p</i>
Age (years)	49.25 ± 5.29	48.86 ± 5.51	<i>t</i> = 0.203	0.245
Duration of ED (years)	2.98 ± 1.96	3.06 ± 1.87	<i>t</i> = 0.611	0.775
BMI (kg/m <sup>2</sup> )	27.33 ± 1.66	27.12 ± 1.63	<i>t</i> = 0.573	0.387
Smoking (cases, %)	25 (61.54)	23 (60.53)	$\chi^2 = 0.160$	0.689
IIEF-5 (values)	10.03 ± 3.01	9.79 ± 3.13	<i>t</i> = 0.338	0.934
25-(OH)D <sub>3</sub> (ng/mL)	18.25 ± 4.93	18.61 ± 4.87	<i>t</i> = 0.695	0.286
T (nmol/L)	11.42 ± 2.76	11.63 ± 2.58	<i>t</i> = 1.225	0.089

ED, erectile dysfunction; BMI, body mass index; IIEF, indexes of international erectile function; 25-(OH)D<sub>3</sub>, 25-hydroxy vitamin D<sub>3</sub>; T, testosterone.

**TABLE 2. Comparison of the clinical data of the two groups.**

Indices	Experimental group (n = 80)	Control group (n = 77)	<i>t</i>	<i>p</i>
GLU (mmol/L)	4.89 ± 0.96	4.76 ± 0.93	0.210	0.227
TC (mmol/L)	4.05 ± 1.12	3.96 ± 0.98	0.604	0.718
TG (mmol/L)	1.03 ± 0.41	1.07 ± 0.39	0.542	0.364
HDL-C (mmol/L)	1.52 ± 0.46	1.48 ± 0.41	0.509	0.303
n-HDL (mmol/L)	2.64 ± 1.23	2.71 ± 1.13	0.347	0.962
VLDL (mmol/L)	0.34 ± 0.10	0.37 ± 0.08	0.701	0.295
LDL-C (mmol/L)	1.98 ± 0.79	2.04 ± 0.65	0.725	0.348

GLU, glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; n-HDL, non-high-density lipoprotein cholesterol; VLDL, very low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**TABLE 3. Comparison within two groups before and after treatment.**

Group	IIEF-5 (values)	25-(OH)D <sub>3</sub> (ng/mL)	T (nmol/L)
Experimental group			
Before treatment	10.03 ± 3.01	18.25 ± 4.93	11.42 ± 2.76
After treatment	17.79 ± 5.23	45.37 ± 5.48	29.41 ± 3.63
<i>t</i>	8.05	9.38	7.84
<i>p</i>	0.00	0.00	0.00
Control group			
Before treatment	9.79 ± 3.13	18.61 ± 4.87	11.63 ± 2.58
After treatment	5.05 ± 5.17	20.13 ± 4.06	12.08 ± 2.65
<i>t</i>	5.03	1.75	0.39
<i>p</i>	0.00	0.67	0.73

IIEF, indexes of international erectile function; 25-(OH)D<sub>3</sub>, 25-hydroxy vitamin D<sub>3</sub>; T, testosterone.

**TABLE 4. Comparison between the two groups before and after treatment.**

Indices	Experimental group (n = 80)	Control group (n = 77)	Statistics	<i>p</i>
Number of patients who were significantly effective (rate)	31 (38.75)	12 (15.58)	$X^2 = 4.99$	0.03
Number of patients who were valid (rate)	39 (48.75)	41 (53.25)	$X^2 = 0.12$	0.73
Number of patients who were invalid (rate)	10 (12.50)	24 (31.17)	$X^2 = 3.94$	0.04
25-(OH)D <sub>3</sub> (ng/mL)	45.37 ± 5.48	29.41 ± 3.63	$t = 8.93$	0.00
T (nmol/L)	20.13 ± 4.06	12.08 ± 2.65	$t = 8.22$	0.00

25-(OH)D<sub>3</sub>, 25-hydroxy vitamin D<sub>3</sub>; T, testosterone.

was statistically significant ( $t = 8.22, p < 0.05$ , Table 4).

#### 4. Discussion

In this present study, we found that low levels of 25-(OH)D<sub>3</sub> were related to ED in the following ways. First, direct inhibition of endothelial cell function: when the levels of 25-(OH)D<sub>3</sub> were low, the inhibitory effect on renin was weakened, *in vivo* angiotensin II increased, the acid adenine dinucleotide phosphate oxidase activity significantly increased, and the formation of super oxygen ions free radicals and super oxygen ions free radicals might have led to a large amount of nitric oxide (NO) consumption in the human body, thus greatly weakened the NO protection of endothelial cells [21–25]. It could also produce an oxidative stress response that eventually leads to ED.

Second, indirect inhibition of vascular endothelial cell function could be achieved through the following ways: (1) Low levels of 25-(OH)D<sub>3</sub> could easily lead to hypertension. Studies have found that the inhibitory principle of 25-(OH)D<sub>3</sub> on angiotensin II was similar to that of angiotensin-converting enzyme inhibitor (ACEI) [26]. In addition, it was previously reported that the risk of hypertension in people with low levels of 25-(OH)D<sub>3</sub> was nearly twice that in people with normal levels [27].

(2) Low levels of 25-(OH)D<sub>3</sub> can increase the risk of diabetes. 25-(OH)D<sub>3</sub> was reported to affect pancreatic islet B cells, leading to an adjustment in the levels of blood glucose in the human body and reducing the levels of 25-(OH)D<sub>3</sub> that can seriously affect the regulation of blood glucose levels in the body to not only create a disorder in blood glucose levels but also increase the body's resistance to organize to insulin, ultimately leading to body sugar metabolic disorder and increasing the risk of developing diabetes [28]. Recent studies showed that people with low levels of 25-(OH)D<sub>3</sub> had a nearly 50% increased risk of developing diabetes than people with normal 25-(OH)D<sub>3</sub> levels [29].

(3) Inflammation and immune response mediated by low levels of 25-(OH)D<sub>3</sub>. It was previously reported that decreasing levels of 25-(OH)D<sub>3</sub> could also increase the expression

of interleukin-6 in vascular endothelial cells, which would impair the function of vascular endothelial cells by inducing the body to enhance inflammatory and immune responses, and eventually lead to ED [30].

(4) In addition, low levels of 25-(OH)D<sub>3</sub> could cause vascular calcification. Vitamin D<sub>3</sub> supplementation can promote the production of fetubulin A, an inhibitor of vascular calcification, and inhibit vascular wall calcification. Further, it was demonstrated that a decrease in the levels of 25-(OH)D<sub>3</sub> could increase vascular calcification [31].

#### 5. Conclusions

This study showed that for ED patients with low levels of 25-(OH)D<sub>3</sub>, the effect of sildenafil combined with vitamin D<sub>3</sub> was significantly better than that of sildenafil alone, demonstrating the synergy between sildenafil and vitamin D<sub>3</sub> in improving patients' 25-(OH)D<sub>3</sub> levels and ameliorating ED and satisfactory safety effects without obvious liver and kidney function damage. No adverse reactions were associated with vitamin D<sub>3</sub> supplementation. The study also suggested that after treatment, the T level of the experimental group was significantly higher than that before treatment. The difference was statistically significant between the two groups, suggesting that vitamin D<sub>3</sub> could effectively increase the content of T in the body, greatly reducing the low serum 25-(OH)D<sub>3</sub> inhibition of gonad function to effectively improve ED.

This is the first clinical study to report the combined application of vitamin D<sub>3</sub> and sildenafil in treating ED in China. The results show that for patients with ED combined with low serum 25-(OH)D<sub>3</sub>, sildenafil combined with vitamin D<sub>3</sub> treatment can significantly improve the low 25-(OH)D<sub>3</sub> status of patients and effectively improve the T level in the body. The treatment outcomes were better than sildenafil alone, with tolerable mild adverse reactions, which could be worthy of clinical application.



## AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding authors.

## AUTHOR CONTRIBUTIONS

XSZ and HJ—designed the research study. KY—performed the research. XSZ and KY—wrote the manuscript. All authors analyzed the data. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was approved by Anqing Hospital of PLA NAVY Ethical Review Board (approval number: Anqing Hospital of PLA NAVY PJ2015-08-01). The patients provided informed consent and agreed to publication of the details of this research.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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