

# BRIEF REPORT

## Promising therapeutic effects of sodium tanshinone IIA sulfonate towards pulmonary arterial hypertension in patients

Jian Wang\*, Wenju Lu\*, Wei Wang\*, Nuofu Zhang\*, Hua Wu\*, Chunli Liu, Xiuqing Chen, Yonghua Chen, Yuqin Chen, Qian Jiang, Lei Xu, Lichun Tian, Pixin Ran, Nanshan Zhong

Guangzhou Institute of Respiratory Disease, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, China

### ABSTRACT

**Background:** Pulmonary hypertension (PH) is a lethal disease with no cure currently available. Sodium Tanshinone IIA sulfonate (STS) is a water-soluble derivative of tanshinone IIA isolated as the major active component from *Salvia miltiorrhiza*, a kind of Chinese herbal medicine. We investigate the efficacy of STS towards treatment of PH patients.

**Methods and results:** Five hospitalized patients were randomly enrolled for this study. These patients were suffering from various types of serious PH without getting sufficient benefits from sildenafil treatment (20 mg tid) for at least three months. The efficacy of STS on PH was evaluated by measuring the pulmonary arterial systolic pressure (PASP), RV size by echocardiography, 6-minute walking distance (6MWD), Borg dyspnea score, and WHO functional class of PH. Patients aged from 17 to 46 (average 33±11) years old, pulmonary arterial systolic pressure (PASP) ranged from 60 to 140 mmHg, RV size ranged from 25 to 39 mm were included in study. At the endpoint of observation for 8 weeks of STS infusion, they obtained reduction of PASP in the range of 14-45 (average 28.6±12.5) mmHg, RV size in the range of 0-10 (average 4.2±1.6). All patients exhibited improved exercise capacity with an increase of 6MWD from 63 to 268 (average 138.4±40.7) meters, significantly reduced Borg dyspnea score from maximum 9 down to 1 or 0, and reduced WHO functional class of PH from III or IV down to II.

**Conclusions:** These results indicate that STS exhibits remarkable beneficiary effects on treating PH patients either alone or in concert with sildenafil.

### KEY WORDS

Pulmonary hypertension; pulmonary arterial hypertension; tanshinone IIA sulfonate

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### Introduction

Pulmonary hypertension (PH) is a life-threatening disease which affects 15 per million adult populations according to a most recent estimation in 2008 (1). It is physiologically defined as an average pulmonary arterial pressure  $\geq 25$  mmHg

at rest, and pathologically characterized by pulmonary vascular remodeling, including smooth muscle hypertrophy and intima thickening. Although significant progress has been made in the past decades in our understanding of PH as well as in disease management, the prognosis is still very poor with an estimated 3-year survival rate in only 72.1% or less if patients without treatment (2-4). Currently, six drugs have been approved in the United States for the treatment of PH. However, none of the approved therapies have shown to be really effective towards the cure of the disease (5). The principal treatments for PH currently rely on different approaches targeting on either the prostacyclin, endothelin or NO pathways (phosphodiesterase inhibition), or increasingly, a combination of them. Moreover, and only very few patients show sensitivity towards treatment with calcium channel blockers (6-11); however, the huge costs and limited efficacy hindered their widespread clinical application.

Sodium tanshinone IIA sulfonate (STS) is a water-soluble derivative of tanshinone IIA isolated as the main pharmacologically

\*J Wang, W Lu, W Wang, N Zhang and H Wu contributed equally to this work.

Corresponding to: Jian Wang, MD. Guangzhou Institute of Respiratory Diseases, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital, Guangzhou Medical University, 151 Yanjiang Road, Guangzhou 510120, China. Email: jianwang1986@yahoo.com; Nanshan Zhong, MD. Guangzhou Institute of Respiratory Diseases, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital, Guangzhou Medical University, 151 Yanjiang Road, Guangzhou 510120, China. Email: nanshan@vip.163.com.

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active natural compound from a traditional Chinese herbal medicine, the dried root of *Salvia miltiorrhiza* Bunge known as Danshen. Danshen has been known for its abilities towards improving body functions such as activating blood circulation and removing blood stasis according to the theory of traditional Chinese medicine (TCM) (12,13). Danshen in the form of injections is also widely and successfully used in China for treating cardiovascular diseases such as coronary heart disease.

To examine if STS exerts beneficial effects on treating PH patients, we performed this pilot clinical trial study, which was conducted according to the provisions of the Declaration of Helsinki, and adhered to local guidelines for good clinical practice.

## Methods

Five patients aged from 17 to 46 (average  $33 \pm 11$ ) years old were enrolled in the present study. These patients were suffering from various types of serious PH with pulmonary arterial systolic pressure (PASP) ranged from 60 to 140 mmHg, RV size ranged from 25 to 39 mm. Two patients have idiopathic pulmonary arterial hypertension; one patient has chronic thromboembolic PH; other two patients have chronic obstructive pulmonary disease (COPD) associated PH. They had been routinely administered with 20 mg sildenafil tablets three times a day for at least 3 months without receiving significant reduction on PASP. A written consent form for this trial was obtained from each of the enrolled patients. All procedures were approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University. The administration of STS was performed strictly according to the guidelines provided by its dispensatory. In the treatments, patients were supplemented with 1 mg/kg/day (iv infusion) STS (Commercial name "Nuoxinkang", manufactured by Shanghai First Biochemistry Pharmaceutical Inc.) diluted by 150 mL NS or 5% GS iv dripped daily on their routine basal treatment with or without sildenafil (20 mg tid). Initially, recruited patients had been hospitalized and given a one-week treatment with STS under intensive observation. Then, those without any side effect during the one-week treatment received a subsequent 7-week infusion of STS according to the therapeutic schedule in hospital or transferred to outpatient department. The efficacy of STS on PH was evaluated by measuring the PASP, RV size by echocardiography, 6-minute walking distance (6MWD), Borg dyspnea score, and WHO functional class of PH.

## Statistical analysis

In this study, each experiment was conducted in triplicate, and the values were expressed as mean  $\pm$  standard error, except that both orthogonal experiments were conducted once. The SAS<sup>®</sup>

system version 9.1 (SAS Institute Inc., Cary, NC, USA) was used for data processing. The MIXED procedure was performed. Values of  $P < 0.05$  were considered to be statistically significant.

## Results

As summarized in Table 1, at the endpoints of observation for 8 weeks of STS infusion, all five patients obtained reduction of PASP in the range of 14-45 (average  $28.6 \pm 12.5$ ) mmHg ( $P = 0.0066$ ), RV size in the range of 0-10 (average  $4.2 \pm 1.6$ ) ( $P = 0.0446$ ). All patients exhibited improved exercise capacity with an increase of 6MWD from 63 to 268 (average  $138.4 \pm 40.7$ ) meters ( $P = 0.0192$ ), significantly reduced Borg dyspnea score from maximum 9 down to 1 or 0 ( $P = 0.1012$ ), and reduced WHO functional class of PH from III or IV down to II ( $P = 0.0005$ ). All the patients cooperated and showed well tolerance towards the treatment throughout the study.

## Discussion

STS has been widely used in oriental countries, especially in China, to treat various circulatory disturbance-related diseases for its pharmacological actions, including vasodilation, anticoagulation, anti-inflammation, and free radical scavenging. Nowadays, Danshen and its various derivatives in numerous pharmaceutical dosage forms are commercially available and commonly administered to treat inflammatory and cardiovascular diseases in various clinics in China with negligible or no adverse effects (14-17). Detailed information about the cardioprotective effects of tanshinone IIA have been discussed in a recent review by Shang *et al.* (18), and Wang (19,20). Previous study from our group and others recently demonstrated that STS exerts protective effects on hypoxic pulmonary hypertension in animals, including lowering pulmonary artery pressure and decreasing the pulmonary artery thickness and right ventricular hypertrophy (20,21). These effects, at least in part were found to be achieved through the regulation of intracellular  $Ca^{2+}$  homeostasis in pulmonary arterial smooth cells (PASMCs) (19,21).

Although STS has been widely used to treat various circulatory disturbance-related diseases for its various logical actions, it is still unknown whether it has beneficial effects on treating PH patients. In the present prospective study, we have, for the first time, demonstrated that STS significantly improved exercise capacity in patients with PH, as assessed by the 6MWT, Borg dyspnea score, and the PASP. An invasive measure by right heart catheterization is quite safe and performed widely in recent years. However, concerning about the risk from this invasive test and an additional expense, as well as no direct therapeutic benefit from this test, most of the patient communications had reluctant to receive a catheterization though many propaganda been made. Some patients was subjected to catheterization

**Table 1.** Effects of STS on variables of PH patients.

Patient	Age/Sex	Time	Variables				
			PASP (mmHg)	RV size (mm)	6 MWD (M)	Borg dyspnea score	WHO functional class of PH
1	17/M	-4 wks/0	104/112	30	---/576.0	---/1	---/III
		8 wks	71	27	651.0	0	II
		Δ (8 wks-0)	-41	-3	75.0	-1	-1
2	32/F	-4 wks/0	87/85	27	---/414.0	---/4	---/III
		8 wks	63	23	477.0	0	I
		Δ (8 wks-0)	-22	-4	63.0	-4	-2
3	38/F	-4 wks/0	138/140	39	---/252.0	---/0	---/IV
		8 wks	128	39	337.0	2	II
		Δ (8 wks-0)	-14	0	85.0	-7	-2
4	33/M	-4 wks/0	82/81	25	---/171.0	---/8	---/IV
		8 wks	61	21	372.0	1	II
		Δ (8 wks-0)	-21	-4	201.0	-7	-2
5	48/F	-4 wks/0	62/60	27	---/130.0	---/7	---/IV
		8 wks	15	17	398.0	2	II
		Δ (8 wks-0)	-45	-10	268.0	-5	-2

PASP, pulmonary arterial systolic pressure; RV, right ventricle; 6MWD(M): 6-minutes walking distance in meters; -4 wks/0: 4 weeks or one day before STS treatment; Δ (8 wks-0): differences between each variables obtained at the time of STS treatment for 8 weeks (designated as time 8 weeks) and at one day before the STS treatment (designated as time 0).

before treatment, but disagreed to receive the second test after the 8-week treatment. So, we could not achieve a strict comparison of right ventricular pressure between pre- and post-treatment using catheterization, which seems a limitation in this study because the invasive measure is thought to provide more precise data. Although, Sonography, turned to be easily accepted by patients for its less injury, lower expensiveness, as well as reliability, catheterization still be the first choice dues to its accuracy property. In addition, we mainly concern the changes of right ventricular pressure pre- vs. post-treatment and the tests had been performed by the same sonographer and equipment to minimize the variants as mentioned above to make sure that the data is comparable. More or less, our study provided very valuable information on STS in the treatment of patients with PH.

### Conclusions

Our results from the present study indicate that STS exhibits remarkable beneficiary effects towards treating PH patients. Considering the long-time use and history of Danshen and its lower cost, STS could be a promising and potentially useful agent for PH treatment which would benefit more PH patients with reduced medical expenses. A large scale clinical trial of STS both alone as well as in combination with other approved medications, including more patients on various types of PH is required.

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