

Sildenafil Reduces Pulmonary Arterial Pressure in Subacute Infantile Mountain Sickness at High Altitude in China: A Pilot Study

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Abstract

Background: Subacute infantile mountain sickness (SIMS) is characterized as severe pulmonary arterial hypertension and right ventricular failure in infants born and living at altitude over 3000 meters. Almost all of the cases were reported from Tibet, and little from other less high altitudes. PDE5 inhibitors appear ideal to treat SIMS by reducing the metabolism of cGMP and increasing NO availability. We assessed the effects of sildenafil on cardiopulmonary hemodynamics in SIMS in Qinghai (average altitude >3000 m).

Methods: Nineteen consecutive children (aged 2-48, median 10 months) were enrolled during 2013 and 2014. They were born and living at altitudes from 2295 to 4400 meters (median 3564 meters). Ten received oral sildenafil 1 mg/kg for 7-10 days (Group S), and 9 did not (Group C). Cardiopulmonary hemodynamics was measured using echocardiography before and after the treatment period.

Results: Before treatment, sPAP was significantly higher in Group S (68.9±9.8 mmHg) as compared to Group C (52.6±12.6 mmHg, P=0.005). sPAP significantly reduced after the treatment in both groups (P_{time}=0.04), but the reduction was significantly greater in Group S as compared to Group C (P_{time*group}=0.045), reaching to a similar level of 40±23 and 39±10 mmHg respectively at the end of treatment. The dimension of the right ventricle decreased significantly in both groups (P_{time}=0.049). There was no significant difference in terms of the overall levels and trends of changes in other variables between the two groups.

Conclusions: Sildenafil significantly reduces pulmonary arterial hypertension in SIMS. Large randomized clinical trials including varied high altitudes are warranted.

Keywords: Subacute infantile mountain sickness; Sildenafil; Pulmonary arterial pressure; High altitude.

Introduction

High altitude hypoxia induces important adaptive cardiopulmonary changes[1,2]. Maladaptation occurs in some conditions resulting in adverse outcomes[3-5]. Subacute infantile mountain sickness (SIMS) is characterized as severe pulmonary arterial hypertension and right ventricular failure mostly in infants born and living at altitude over 3000 meters[6-8]. In China, it came into prominence after sudden migration of the large numbers of Han Chinese population from the low altitude of mainland to the high altitudes in 1950s and 1960s, and almost all of the cases were reported from Tibet (average altitude 4900 meters)[8-10]. The number of cases has been substantially reduced since the increasing of awareness of the disease and many Han mothers in Tibet descent to lowland to give birth since 1980s^[8]. However, paucity of data exists about its characteristics in other less high altitude regions, such as Qinghai province (average altitude >3000 meters)[11]. We have recently reported that healthy children born and living in Qinghai province, as compared to those at sea-level, have distinctive adaptive features with a significantly higher pulmonary arterial pressure, dilated right heart, slower regression of right ventricular hypertrophy with reduced systolic and diastolic function of both ventricles, indicating the susceptibility to SIMS[2].

In SIMS, sustained hypoxia leads to pulmonary endothelial dysfunction, a reduction of nitric oxide, hypertrophy of muscular pulmonary arteries and muscularization of pulmonary arterioles[12,13]. The phosphodiesterases5 (PDE5) inhibitors appear ideally suited to treat high altitude pulmonary arterial hypertension, with their effects to reduce the metabolism of cyclic GMP, thereby extending and amplifying the effect of existing NO production[14]. The distribution of PDE5 is found abundant throughout the muscularized pulmonary vascular tree, including the distal pulmonary arterioles as well as in hypertrophied myocardium induced by pressure overload[15-17]. PDE5 inhibitors have been reported to reduce pulmonary arterial pressure (PAP) and increase exercise capacity in acute hypoxic models, simulated or accenting to high altitude models including animals and humans[16,18-20]. There have been fewer reports about sildenafil treatment in patients residing at high altitudes[15]. A study in newborn sheep showed that highland sheep, as compared to the lowland ones, were more sensitive to sildenafil with greater blunting of pulmonary arterial hypertension[17]. In a human study by Aldashev et al. [15] oral sildenafil significantly reduced high altitude pulmonary arterial hypertension (mPAP>25 mmHg) in otherwise healthy adults[15]. No data exists on the effects of PDE5 inhibitors in SIMS. Therefore, the aim of our study was to assess the effects of sildenafil on cardiopulmonary

hemodynamics in SIMS patients in Qinghai province, China.

Patients and Methods

Patients: The study was prospectively conducted in 2013 and 2014 in accordance with research protocols approved by the Institutional Research Ethics Boards at Qinghai Women's and Children's Hospital in Xining, the Capital of Qinghai province. During the two years, there were 4800 patients admitted to the pediatric intensive care unit (PICU), and 30 of them were diagnosed with SIMS, making the prevalence of 0.63%. Among them, 11 were not enrolled in the study because they did not have echocardiography assessments either prior to or after the treatment. A total of 19 consecutive children (aged 2 to 48 months, median 10 months) were studied. The patients were born and living at altitudes ranging from 2295 to 4400 meters (median 3564 meters). Most patients were brought to the PICU because of dyspnea and cough. Other common symptoms were sleeplessness, irritability, cyanosis and edema of the face. The salient features on clinical examination were tachypnea, enlargement of the liver and rales in the lungs.

PICU management: High flow oxygen mask (5 L/min, oxygen concentration 40%) was used. Arterial oxygen saturation was maintained at 95±4.5%. Clinical routine management included cardiotoxic support with intravenous digitalis (0.03mg, per 12 hours), diuretic therapy with furosemide (0.5 mg/kg, per 12 hours) and systemic vasodilatation with phentolamine (5 µg/kg/min) for 7-10 days. Some of the clinicians started to use sildenafil (Pfizer Pharmaceutical Co. Commodity name: Viagra, specifications: 100 mg/ tablet, batch number: H20020527) 1 mg/kg (divided into 3 times per day) since the beginning of 2013, while some others did not. There was no standard protocol in the use of sildenafil in the PICU.

Methods of Measurements

Patient monitoring: All patients had continuous monitoring of heart rate and systemic arterial pressure.

Echocardiography Assessments of Cardiopulmonary Hemodynamics

Systolic pulmonary arterial pressure (sPAP): A Phillips-7500 (Phillips, Amsterdam, the Netherlands) was used to measure the peak velocity of tricuspid regurgitation jet to estimate gradient of systolic right ventricular pressure and right atrial pressure. This gradient was increased by 10 mmHg to estimate sPAP.

Cardiac function: Diastolic function of the right and left ventricles used the ratios of E wave and A wave peak velocities of the tricuspid and mitral valves respectively (E/A_{TV} and E/A_{MV}). Systolic function of the left ventricle used left ventricular ejection fraction (LVEF) and cardiac output index (CI) using the modified Simpson method. The dimensions of right ventricle (RV) and main pulmonary artery (PA), left ventricle in systole and diastole (LVs and LVd) were obtained using standard views.

Study protocol: The use of sildenafil varied among clinicians in clinical practice in the PICU, rather than being randomized in the study. Among the 19 patients, 10 received sildenafil for 7-10 days (Group S), and 9 did not and served as control group (Group C). Measurements were made prior to and at the end of the 7-10 days treatment period. The echo cardiographer was blinded to the assignment of study groups.

Statistical analysis: Data were described as mean±standard deviation or range with median. Un-paired t-test was used to examine the differences in continuous demographic variables and clinical variables prior to treatment between the two groups. Chi-squared test was used to examine the difference in the constant demographic variables including gender and ethnics between the two groups. Mixed linear regression analysis for repeated measures was also used to compare the changes of each of the variables between the two groups during the study period. The parameter estimates and P values of time (P_{time}) indicate the significance of the changes before and after the study period in the two groups. The parameter estimates and P values of group (P_{group}) indicate the significance of the general differences of the variables between the groups. The parameter estimates and P values of the interaction of time and group ($P_{group*time}$) indicate the differences in trends of the variables during the study period between the two groups. All data analysis was performed using SAS statistical software version 9.3 (SAS Institute, Inc, Cary, NC). A P value < 0.05 indicated a statistical significance.

Results

Demographic data: There was no significant difference in age between Group S and Group C (12.8 ± 15.9 and 9.6 ± 3.0 months respectively, $P=0.55$), body weight (6.3 ± 3.3 and 6.8 ± 1.5 kg respectively, $P=0.74$), distributions of gender (7 boys and 3 girls in Group S, and 7 boys and 2 girls in

Group C, $P=0.56$), ethnicity (5 Hans and 5 Tibetans in Group S, and 4 Hans and 5 Tibetans in Group C respectively $P=0.59$) and altitude (3535 ± 638 and 3756 ± 511 meters respectively, $P=0.41$). All patients survived. Symptoms and clinical features were improved in both groups. The duration of PICU stay was 10 ± 1.3 and 10 ± 3.6 days in Group S and Group C respectively ($P=0.811$).

Comparison of the Changes in Cardiopulmonary Hemodynamics between the two Groups during the Study Period:

Prior to treatment, sPAP was significantly higher in Group S (68.9 ± 9.8 mmHg) as compared to Group C (52.6 ± 12.6 mmHg, $P=0.005$). There was no significant difference in any other variables between the two groups. sPAP significantly reduced after the treatment in both groups ($P_{time}=0.04$), but the reduction was significantly greater in Group S as compared to Group C ($P_{time*group}=0.045$), reaching to a similar level of 40 ± 23 and 39 ± 10 respectively at the end of the study period. The dimension of the right ventricle reduced significantly in both groups ($P_{time}=0.049$), without significant difference in the levels and the trends between the two groups. No significant difference was found in any other variables in terms of the overall levels and the changes during the study period in the two groups, including systemic arterial pressure. No difference was found between the Hans and the Tibetans in any of the variables ($P>0.20$ for all).

Discussion

This pilot study demonstrated the beneficial effects of oral sildenafil therapy in SIMS. The initial sPAP prior to treatment was significantly higher in Group S as compared to Group C. After treatment with sildenafil for 7-10 days, the reduction in sPAP was significantly greater in Group S as compared to Group C, reaching to a similar level between the two groups. Systemic arterial pressure remained stable during the treatment with sildenafil.

SIMS is classically characterized by features of severe hypoxic pulmonary arterial hypertension and right heart failure mainly in infants and young children living at high altitude over 3,000 meters. It has been reported in Tibet, China [8-11] and other high altitude regions worldwide [6-8]. In China, it came into prominence after sudden migration of the large numbers of Han population from the low altitude of mainland China to the high altitudes, particularly in Tibet in 1950s and 1960s. With an average altitude of 4,900 meters, Tibet is the highest region on earth and commonly referred to as the "Roof of the World".

The first case was reported in 1955 showing that a Han infant aged 11 months, born in Lhasa, the Capital of Tibet (3,658 meters), who presented at month 9 with dyspnea, cyanosis and signs of severe right heart failure, with peripheral edema, liver enlargement, and ascites. Medical treatment was ineffective. Despite descending to sea level, the infant died[9]. Following this, a number of studies were reported from Lhasa through 1960s to 1980s[8-10]. The prevalence was high, accounting for 4.6% of all pediatric patients and of 42.6% of the pediatric cardiac disease patients hospitalized during that period[11,12]. The condition was usually fatal within a few months. Most of the patients were Han Chinese. The increasing awareness of the syndrome has led Han mothers to descend to lower altitudes to give birth and not bringing them back, and consequently, the prevalence of the disease decreased rapidly. Since then there have been few reports about this disease. Little attention has been paid to other less high altitude regions in China, including Qinghai province where the average altitude is above 3000 meters[11], likely due to relatively less prevalence and less severe condition. As shown in our study, the prevalence in PICU was 0.63%, and none of the patients died during hospitalization.

The key feature in the pathogenesis of SIMS is excessive pulmonary arterial hypertension. Nonetheless, the direct measurements of pulmonary arterial pressure by cardiac catheterization are limited. Khoury and Hawes reported five cases from Denver and Leadville, Colorado, USA (1600 and 3100 meters respectively) (age ranged from 6 to 18 months); the average values for systolic, diastolic, and mean pulmonary arterial pressures were 71 ± 6 mmHg, 30 ± 6 mmHg, and 47 ± 6 mmHg, respectively[6]. Grover et al. [7] described a case of a 15-year-old Caucasian girl residing at Leadville who had a grossly elevated PAP [$67/24$ (44) mmHg][7]. Wu et al. [11] measured the mPAP by cardiac catheterization in Xining (2261 m) in 8 children on recovery from subacute infantile mountain disease (within 2 weeks after admission), mPAP was 33 ± 11 mmHg[11]. In our study, the initial sPAP by echocardiography in Group S was significantly higher (68.9 ± 9.8 mmHg) as compared to Group C (52.6 ± 12.6 mmHg, $P=0.005$). The sPAP level in Group S is close to previous reports. Treatment with sildenafil was associated with a significantly greater reduction in sPAP, reaching to a similar level of about 40 mmHg in the two groups. This value is close to Wu et al's report[11]. Our data indicates the beneficial effect of substantial pulmonary vasodilatation of the PDE5 inhibitor.

The pathophysiology of pulmonary arterial hypertension in SIMS is due to exaggerated hypoxic pulmonary vasoconstriction and adverse remodeling of pulmonary arteries[10]. The vascular remodeling involves all cellular elements of the vessel wall with endothelial dysfunction, extension of smooth muscle into previously non-muscularized vessels, and adventitial thickening[8,21]. The biochemical pathways underlying this pathophysiology remain poorly understood, but a reduction in nitric oxide production may have a role. Nitric oxide has vasorelaxant and anti-proliferative effects which are

mediated by cGMP, and cGMP is hydrolyzed by PDE[14]. More interestingly, the distribution of PDE5 is found abundant throughout the muscularized pulmonary vascular tree after exposed to hypoxia, including in distal pulmonary arterioles[15-17]. This offers the mechanism of relatively selective pulmonary vasodilatation with little systemic hypotension. PDE5 inhibitors reduce PAP in acute hypoxic models including animals and humans [16,18-20]. There have been few reports about sildenafil treatment at high altitudes[15]. An animal experiment showed that highland newborn sheep were more sensitive to sildenafil with a greater blunting of pulmonary arterial hypertension[17]. In a human study by Aldashev et al. [15], high altitude pulmonary arterial hypertension (mPAP > 25 mmHg) was screened from otherwise healthy adults in the Naryn region of Kyrgyzstan (2500–4000 meters). Notably, the Naryn region is in the Himalayan range that includes Qinghai-Tibet plateau. Oral sildenafil treatment for 3 months significantly reduced mPAP by 6.7 mmHg as compared to the placebo group. Our study is the first, to our knowledge, to demonstrate the effectiveness of sildenafil to reduce PAP in SIMS. It should be noted that our data did not show any significant difference in PAP or other variables between the Hans and the Tibetans before and after the study period. This is different from previous reports showing minimal elevation of pulmonary artery pressure with higher nitric oxide concentration in exhaled breath in Tibetans[22] and substantially high prevalence in the Han children as compared to the Tibetans[8 - 10]. But our finding in the present study is consistent with our previous report that showed no significant difference in cardiopulmonary adaptations between the Han and the Tibetan healthy children born and living in Qinghai province[2]. Furthermore, in a number of clinical trials in patients with congestive heart failure[23-25], the greatest benefit of PDE5 inhibitors in cardiac performance have been found in patients with secondary pulmonary arterial hypertension and right ventricular failure[24,26]. In our study, CI and other cardiac functional variables did not show any significant difference in Group S as compared to Group C during the study period, and the reduction in right ventricular dimension at the end of the study period was to a similar degree between the two groups. This might be due to the small number of patients and lack of strict randomization in our design.

Finally, we did not observe any obvious side effects on systemic vasculature. Systemic arterial pressure remained stable in our patients.

Clinical implications: Our study has important clinical implications. More than 140 million people worldwide live above 2500m altitude. Of them, 80 million live in Asia. Although the prevalence of SIMS rapidly decreased in Tibet, it is not uncommon and remains a critical illness although usually not fatal in other regions at less high altitudes including Qinghai province[8] and other ethnic populations such as Kazakh and Muslim[27].

Additionally, there are other forms of mountain-related illness, such as adult subacute mountain sickness and chronic mountain sickness, which share similar mechanisms as SIMS [8,28,29]. In these patients, treatments are limited, and inhalation of oxygen is ineffective[30]. Therefore, sildenafil therapy may have an important role.

Limitations: This is a pilot study in a small number of patients in a single center. The important limitation is the lack of strict randomization. Rather, the patients were grouped according to the varied individual clinician's practice and there was no standard protocol in the use of the sildenafil. It has been increasingly realized that variability in patterns of clinical practice reflects minimal in terms of an

evidence base. Additionally, follow-up data remains to be collected in these patients. Large randomized clinical trials including varied high altitudes and ethnic populations are warranted to verify efficacy, tolerance and safety and long term effects of PDE5 inhibitors.

Conclusions

Oral sildenafil significantly reduces pulmonary arterial hypertension in subacute infantile mountain sickness. It has little effect on systemic arterial pressure. Larger randomized clinical trials including varied high altitudes and ethnic populations and long term follow-up are warranted.

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