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ORIGINAL ARTICLE

Bosentan versus nifedipine in the treatment of vasculopathy in systemic sclerosis patients: A randomized control trial

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Abstract

Background: Bosentan is effective agent in scleroderma vasculopathy. However, there are no studies evaluating effectiveness of bosentan in Vietnamese patients, where nifedipine is still the common treatment.

Objective: To compare the efficacy of bosentan versus nifedipine in scleroderma vasculopathy in Vietnamese patients.

Methods: We randomly assigned 70 patients in a 2:1 ratio to receive oral bosentan or oral nifedipine for 16 weeks, respectively. The primary outcomes were the change in Raynaud's Condition Score (RCS), appearance of new digital ulcers (DUs) and change in World Health Organization (WHO) functional class. Secondary outcomes were the change in the nailfold capillaries disease stage and systolic pulmonary arterial pressure (sPAP) value.

Results: At week 16, patients in bosentan group had no RCS imprvement, the mean difference was 0.8 ± 0.2 (95% CI, 0.4 to 1.1, $p < 0.001$) and improved WHO functional class, a mean treatment effect of 35.6% in favor of bosentan (95% CI, 13.4 to 57.7%, $p < 0.05$). Bosentan treatment was associated with a 58% reduction in the number of new DUs compared with nifedipine (mean ± standard error: 0.22 ± 0.42 vs 0.52 ± 0.59 new DUs, $p < 0.05$). sPAP was decreased by 4.1 ± 3.8 mmHg (95% CI, 3.0 to 5.3, $p < 0.001$) in bosentan group, versus 1.0 ± 2.9 mmHg (95% CI, -0.2 to 2.1, $p > 0.05$) in nifedipine group. Headache was the most common adverse event in both groups.

Conclusions: Bosentan significantly limited the occurrence of new DUs, reduced symptoms of pulmonary arterial hypertension and sPAP value and all were better than nifedipine.

Key words: bosentan, vasculopathy, Raynaud, digital ulcers, pulmonary arterial hypertension

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Introduction

Systemic sclerosis (SSc) is a rare autoimmune disorder with multi-organ involvement. Although SSc is considered a fibrosing disease, vascular involvement plays a major role in pathogenesis and organ dysfunction.[1] SSc involves both peripheral and central vascular systems that seriously affect quality of life and functional activities of patient.[2]

Nifedipine, a classical calcium channel blocker (CCB), are still the most commonly used agents for Raynaud's phenomenon (RP) and DUs management in SSc and also was commended as one of the first-line treatment option for RP.[3-5] However, nifedipine was not a good choice for DUs and pulmonary arterial hypertension (PAH).[6-8]

Endothelin-1 is a potent endogenous vasoconstrictor and smooth-muscle mitogen that acts through 2 receptors, endothelin A (ETA) and endothelin B (ETB).[9] Increased endothelin-1 activity has been considered to have a key role in the pathogenesis of the vascular component, especially in pulmonary arterial hypertension.[2,7,9-12] Bosentan is a dual

endothelin-1 receptor antagonist. Bosentan was approved by the U.S. Food and Drug Administration for WHO functional class III and IV PAH and reducing number of new DUs in patients with SSc.[13,14] However, bosentan did not promote the healing of existing DUs and there is ongoing debate in respect of its use in RP secondary to SSc.[15-17]

The aim of this study was to compare the efficacy of bosentan versus nifedipine in the treatment of peripheral vascular diseases and PAH in Vietnamese systemic sclerosis patients.

Methods

Study design and populations

The study was conducted between August 2020 and July 2021 at autoimmune connective tissue disease unit of National Hospital of Dermatology and Venereology in Vietnam and was reported in the line with the CONSORT guidelines. This study was designed as a non-blinded, randomized, active-controlled trial. All 70 patients were randomly assigned in a 2:1 allocation ratio to receive oral bosentan or nifedipine, respectively.

The study focused on adult systemic sclerosis patients who were diagnosed according to ACR/EULAR classification.[18] For ethical reasons, eligible patients in class IV were also required to have a sufficiently stable clinical status to enable them to participate in this study. The inclusion criteria includes a estimated resting sPAP greater than 35 mm Hg on transthoracic echocardiogram (TTE), having at least one of the following: RP, active DUs, digital pitting scars. Patients were excluded if they had had started or stopped any therapy for pulmonary arterial hypertension within one month before screening, had contraindications of bosentan including hypersensitivity to bosentan, moderate to severe hepatic impairment (i.e., Child-Pugh class B or C), baseline values of liver aminotransferases (i.e., aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), greater than 3 × the upper limit of normal), concomitant use of cyclosporine A, pregnancy and women of childbearing potential who are not using reliable methods of contraception. Patients were asked to use reliable methods of contraception during the study.

Randomization and intervention

All participants were provided detailed information about the study by the researcher and completed the written informed consent. The randomization process to assign the 2 treatment groups was conducted as follows: 1) the patients, with their study number, drew a sealed card from the box which had 50 bosentan cards and 25 nifedipine cards. Patient in bosentan group was receive 62.5 mg of oral bosentan twice daily for 4 weeks followed by 125 mg twice daily for 12 weeks. Patient in nifedipine group was receive 20 mg of oral nifedipine (modified release tablets) twice daily for 16 weeks. By the end of the enrollment period, 70 patients were recruited into the study.

Outcome and safety assessments

The primary end points in this study were degree of change in Raynaud's Condition Score (a measure of Raynaud's influent on a scale of 0 to 10, with higher values indicating more difficulty; evaluated by subjective assessment), appearance of new digital ulcer (evaluated by subjective and objective assessment) and WHO functional class (a modification of the New York Heart Association class, with higher classes indicating more severe disease; evaluated by subjective and objective assessment). The secondary end point was change in the sPAP value. Measurements were performed at 2 points of time: baseline and at the end of the sixteenth week. sPAP value was estimated by TTE by Vivid S70N (Philips®, Netherlands) (based on availability of TTE and nonroutine indication of right heart catheterization). Clinical examination and subjective assessment were evaluated by two independent physician in every visit. Subclinical examinations were evaluated at the same faculty.

Clinical examination, complete blood count, biochemistry tests (including blood urea nitrogen, creatinin, AST, ALT, albumine), rapid detection pregnancy test for female patient of childbearing potential were performed every 4 week to evaluate adverse events. Patients are required to notify investigator immediately of any abnormal symptoms. Patients who have liver aminotransferases value greater than 3 × the upper limit of normal or have any intolerant symptoms or develop right heart failure, were withdrawn from the study. These patients will be treated by other routine treatments at our facility. All patients were transferred to Vietnam national heart institute when they developed right heart failure.

Statistical analysis

Statistical methods were calculated using IBM SPSS Statistics for Windows, version 20 (IBM Crop). All continuous data were presented as mean; independent t-test and paired t-test were used to compare between group and same group means, respectively. All categorical data were reported in percentage. Clinical data and disease variables were analyzed and compared between groups by calculating 95% confidence interval (CI) univariate regression analyses to assess the significant difference. The chi-squared test and Fisher's exact test were used for the comparison. P-values less than 0.05 were considered significant.

Ethical approval

The research proposal was approved by the Ethical Review Board of National Hospital of Dermatology and Venereology. The study was explained to all respondents willing to participate in it and all participants granted their consent before participating in the study. All participants signed the informed consent. All participants had the right to withdraw from the study at any time.

Results

Seventy patients were enrolled into this study in a 2:1 allocation ratio. The intervention were performed in all patients with no drop out of participants. CONSORT flow chart is shown in **Figure 1**.

Baseline demographic, clinical and subclinical characteristics of the patients are described in **Table 1**, which showed no statistical significance except for FVC measurement (mean values were 74.6 ± 16.7% in bosentan group and 84.4 ± 19.7% in nifedipine group, $p = 0.042$).

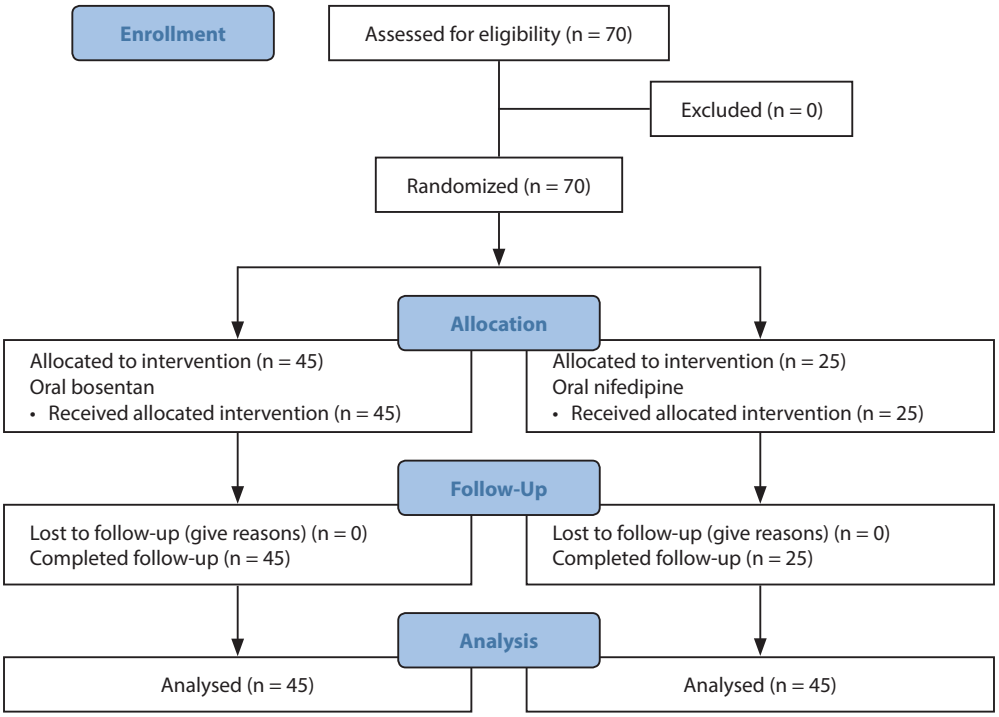

Figure 1.

Table 1. Demographic, clinical and subclinical characteristics of the patients at baseline

Characteristic	Bosentan group (n = 45)	Nifedipine group (n = 25)	*p* value
Age – yr	52.1 ± 11.8	56.0 ± 12.1	0.200*
Female sex – no. (%)	33 (73.3)	19 (76.0)	0.414†
Duration of SSc – mo	43.9 ± 42.0	34.1 ± 30.8	0.269*
SSc types			
dcSSc – no. (%)	29 (64.4)	19 (76.0)	0.632‡
lcSSc – no. (%)	15 (33.3)	6 (24.0)	
other – no. (%)	1 (2.2)	0 (0.0)	
Nailfold capillaries disease – no. (%)	45 (100.0)	25 (100.0)	
Early stage	23 (51.1)	11 (44.0)	0.453†
Active stage	10 (22.2)	9 (36.0)	
Late stage	12 (26.7)	5 (20.0)	
Raynaud's phenomenon – no. (%)	44 (97.8)	25 (100.0)	1.000‡
Raynaud's Condition Score - points	3.8 ± 1.6	4.2 ± 1.1	0.287*
Active digital ulcers – no. (%)	6 (13.3)	3 (12.0)	0.482*
Digital pitting scars – no.	1.0 ± 1.4	1.1 ± 1.2	0.802*
Interstitial lung disease – no. (%)	45 (100.0)	24 (96.0)	0.357‡

Table 1. Continued

Characteristic	Bosentan group (n = 45)	Nifedipine group (n = 25)	*p* value
FVC - %	74.6 ± 16.7	84.4 ± 19.7	0.042*
Systolic pulmonary arterial pressure values - mm Hg	40.8 ± 6.0	39.0 ± 2.5	0.082*
WHO functional class – no. (%)			
I	12 (26.7)	5 (20.0)	
II	21 (46.7)	17 (68.0)	
III	12 (26.7)	3 (12.0)	0.196†
IV	0 (0.0)	0 (0.0)	

*Independent Samples t Test; †Chi-square test; ‡Fisher's exact test; ±values are means SD
WHO denotes World Health Organization; SSc denotes Systemic Sclerosis; FVC denotes Forced Vital Capacity

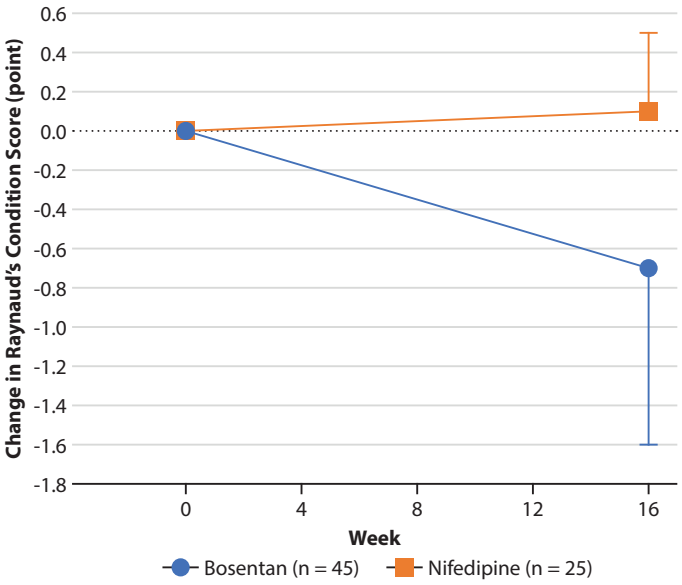

Figure 2. Mean (±Standard Error) change in RCS from Baseline to Week 16 in the Bosentan (circles) and Nifedipine (squares) Group. *P* < 0.001 for the comparison between the bosentan and nifedipine by the Independent-Samples T Test.

After 16 weeks of treatment, RCS was decreased by 0.7 ± 0.9 (95% CI, 0.4 to 1.0, $p < 0.001$) in the bosentan group, whereas RCS was increased by 0.0 ± 0.6 (95% CI, -0.3 to 0.2, $p > 0.05$) in the nifedipine group, a mean different of 0.8 ± 0.2 (95% CI, 0.4 to 1.1, $p < 0.001$; **Figure 2**); both do not have Minimally Important Difference.[19] After treatment, patients in bosentan group developed 10 new DUs, while this number in nifedipine group was 13. After bosentan treatment, there was a 58% reduction in the occurrence of new DUs compared with nifedipine in the study population (0.22 ± 0.42 vs 0.52 ± 0.59 new DUs, $p = 0.031$; **Figure 3**).

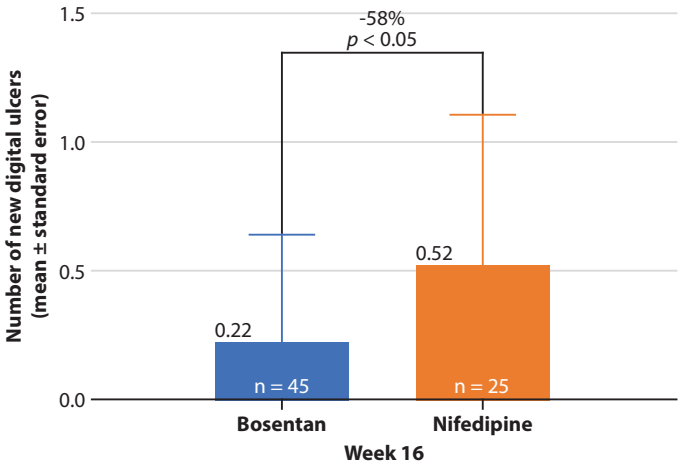

Figure 3. Mean number (±Standard Error) of new digital ulcers in the study population at week 16. *P* < 0.05 for the comparison between the bosentan and nifedipine by the Independent-Samples T Test.

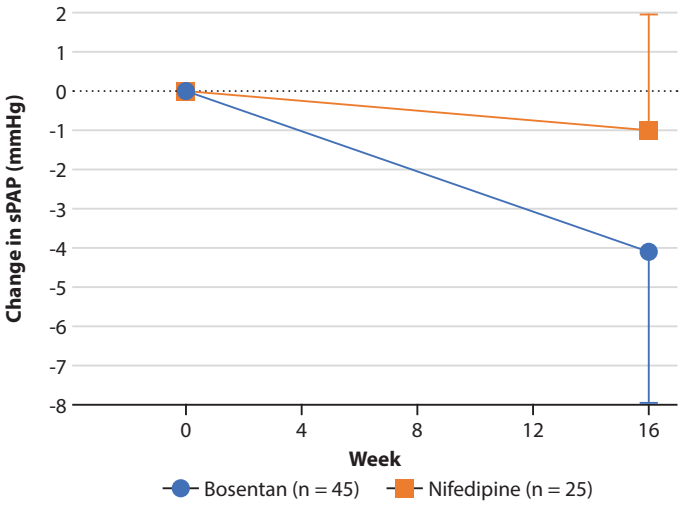

Figure 4. Mean (±Standard Error) Change in sPAP in patients with SSc receiving bosentan (circles) and those receiving nifedipine (squares) at baseline and at the end of the follow-up period at week 16. *P* < 0.001 for the comparison between the bosentan and nifedipine by the Independent-Samples T Test.

sPAP value was decreased by 4.1 ± 3.8 mmHg (95% CI, 3.0 to 5.3, $p < 0.001$) in the bosentan group after 16 weeks, whereas a deterioration of 1.0 ± 2.9 mmHg (95% CI, -0.2 to 2.1, $p > 0.05$) occurred in the nifedipine group, a mean different of 3.2 ± 0.7 (95% CI, 1.8 to 4.6, $p < 0.001$; **Figure 4**). In WHO functional class, 55.6% of the bosentan-treated patients and 20.0% of the nifedipine-treated patients were in a better functional class at week 16 than at base line, resulting in a mean treatment effect of 35.6% in favor of bosentan (95% CI, 13.4 to 57.7%, $p < 0.05$; **Figure 5**).

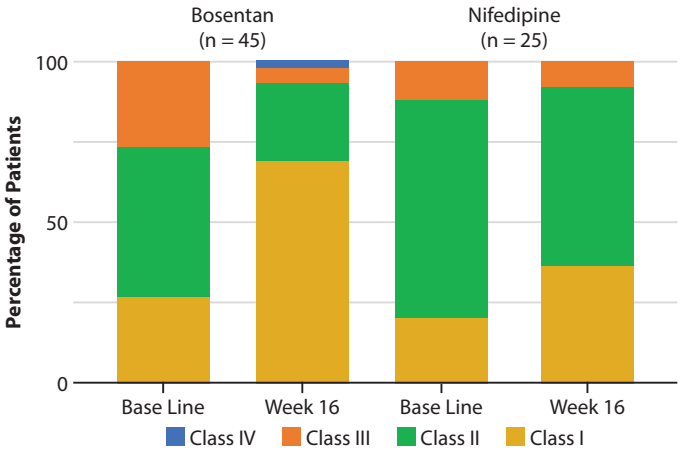

Figure 5. Change in World Health Organization Functional Class from Base Line to Week 16 in Bosentan and Nifedipine Groups. Higher classes indicate a greater severity of disease.

Headache was the most common adverse event in both groups, 6.7% and 4.0% in the bosentan and nifedipine groups, respectively, with no significant difference between the two groups ($p > 0.05$). In bosentan group, edema occurred in 2 patients (4.4%) and elevated liver enzymes occurred in 1 patient (2.2%; 2 times the upper limit of normal); but there was no statistical difference with the nifedipine group with $p > 0.05$. No adverse effects that interrupted the study was reported.

Discussion

Vasculopathy in SSc is characterized by vasoconstriction, adventitial and intimal proliferation, inflammation, and thrombosis.[3,5,20] Pathological changes occurred in both peripheral and central vascular systems. The manifestations of peripheral vascular disease in SSc patients range from episodic RP, the earliest and most common manifestation,[21,22] to irreversible tissue injury with DUs and gangrene that seriously affect quality of life and functional activities of patient.[1,7,8] Meanwhile, PAH is the most important concern in central vascular system which is currently the most common cause of disease-related death in SSc.[1,12,23,24] In this study, we evaluated the efficacy of drugs in most of the important aspects of vasculopathy in scleroderma and we also noted the good efficacy of bosentan, which is an antagonist of both endothelin A and endothelin B receptors with a slightly higher affinity for ETA receptor than for ETB receptor.[14]

For RP secondary to SSc, nifedipine was still commended as one of the first-line treatment options,[4,5,25] was also the most commonly used agents for RP management in SSc, including Vietnam. Meanwhile the use of bosentan as first choice in RP secondary to SSc is still controversial.[15,16] In our study, patients in bosentan group did not have improvement in RP as scored by RCS based on Minimally Important Difference,[19] and this is similar to nifedipine treatment. This results unlike other studies of Hettema et al[26] and Parisi,[27] which had the same dose of bosentan and treatment period as our study. Relative long course of the disease as well as progressive capillary injuries on capillaroscopy partly explain possibly this minimal response. Active stage of nailfold capillary disease detected by nailfold capillaroscopy is characterized by frequent giant capillaries, frequent capillary hemorrhages, moderate loss of capillaries, mild disorganisation of the capillary architecture, absent or mild ramified capillaries while late stage is characterized by irregular enlargement of the capillaries, few or absent giant capillaries and hemorrhages, severe loss of capillaries with extensive avascular areas, disorganisation of the normal capillary array and ramified or bushy capillaries.[28,29] In our study, active and late stage accounted for approximately 50% of patients in both groups, which reflects significantly peripheral vasculopathy and predicts modest responses.[28,29]

Unlike RP treatment, bosentan have proved to be an effective treatment option in preventing new DUs without promoting the healing of existing ulcers by some randomized placebo-controlled studies.[15,17,25] Meanwhile, the efficacy of nifedipine in DUs is less clear.[6,30] In our study, bosentan treatment was associated with reducing number of new DUs as bosentan's widely accepted indication, which is superior to nifedipine treatment.

Bosentan improved exercise capacity and symptoms in SSc-PAH patients with WHO functional class III and IV through randomised double-blind, placebo-controlled studies and was approved by the FDA for this indication.[13,14,31,32] Whereas, high-dose CCBs therapy is unlikely to be indicated in SSc-PAH since vasodilator-responsive PAH is a very rare occurrence in SSc patients (approximately 2 percent) and the response is unlikely to be sustained; not to mention its nonspecific systemic vasodilation side effects of high dose.[7,8,30] There is the same result in our study, in which bosentan significantly improved WHO functional class and was superior to nifdedipine although patients in both groups mainly had WHO functional class II. In this study, sPAP was also significantly decreased in bosentan group compared with that in the nifedipine group. This result is different from some other studies in which there was no change in pulmonary artery pressure after 6-month[33] and 18-month[34] treatment of bosentan. This may be a limitation of our study because right heart catheterization, gold standard for PAH diagnosis,[35] was not done to evaluate sPAP.

The tolerability of bosentan was good and there were no discontinuations in our study. Headache was the most common adverse event in both groups with no significant difference between the two groups. In bosentan group, edema occurred in 2 patients (accounted for 4.4%) and elevated

liver enzymes in 1 patient (accounted for 2.2%); but there was no statistical difference with the nifedipine group. No adverse effects that interrupted the study was reported. The rate of elevated liver enzymes were low in our study without elevation above 3 times the upper limit of normal. Other common side effects such as anemia, dizziness, and flushing were not found in our study.

The limitations of this study included: 1) small population enrollment, 2) short duration of follow-up, 3) TTE is not a gold standard method for PAH and 4) measurement bias with simple randomization.

Conclusion

With good tolerability, bosentan is an useful treatment for preventing new DUs and reducing symptoms of PAH in Vietnamese patients with SSc. Bosentan is a good alternative to nifedipine, which is still main treatment for vasculopathy of SSc in Vietnam.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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