EFFICACY AND SAFETY OF INTRAVENOUS ILOPROST IN THE TREATMENT OF RAYNAUD'S PHENOMENON AND DIGITAL ULCERS IN PATIENT WITH SYSTEMIC SCLERODERMA

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SUMMARY

Objectives: To evaluate the efficacy and safety of intravenous iloprost in the treatment of Raynaud's phenomenon and digital ulcers in patients with SSc (systemic scleroderma).

Methods: 31 patients with SSc were treated with intravenous iloprost in NHDV from April, 2017 to March, 2020. Evaluation was done after 2 weeks and included: width of ulcer, depth of ulcer, Raynaud phenomenon, laboratory tests, drug side effects.

Results: VAS of Raynaud's syndrome decreased markedly after iloprost infusion, from 71.5 points to 36.9 points. ($p < 0.001$). The depth of ulcer improved markedly after 2 weeks of treatment, the rate of deep ulcers decreased from 20.6% to 1% ($p < 0.001$). The ulcer width improved significantly after 2 weeks of treatment, the rate of grade 3 ulcers decreased from 35.1% to 13.4% ($p < 0.001$). Side effects were found in 38.7% of patients, mainly headache (25.7%), flushing (9.7%); nausea/vomiting (6.5%); reaction at the site of infusion (6.5%). All side effects disappear when the infusion rate reduced. The majority of patients tolerated the drug at the maximum infusion rate (level 4), accounted for 61.3%.

Conclusion: Intravenous iloprost is an effective and safe drug in the treatment of Raynaud's phenomenon and digital ulcers in patients with SSc. The infusion process should be monitored according to the instructions.

Keywords: *Systemic sclerosis, Raynaud phenomenon, Digital ulcers, Iloprost.*

1. INTRODUCTION

Systemic sclerosis is an autoimmune connective tissue disease, the second common after systemic lupus erythematosus [1], with unknown etiology, chronic course, and difficult treatment.

Vasculopathy is an important feature in the pathogenesis and clinical manifestations of SSc. The earliest manifestation of vasculopathy is peripheral vascular damage causing Raynaud's phenomenon, digital ulcers that greatly affect on quality of life and cause life-threatening complications [2]. Treatments include non-pharmacological method such as avoidance of triggers, local ulcer care and medication such as antibiotics, vasodilators and surgery with severe lesions.

Iloprost is an isomer of prostaglandin. Beside vasodilating effects, it also stimulates fibrinolysis and inhibits platelet aggregation. In Europe, SSc patients who suffer from digital ulcers are treated with iloprost to improve and prevent of lesions [3].

In Vietnam, the studies on iloprost are very few and mainly applied on the treatment of pulmonary arterial hypertension. Meanwhile, Raynaud's phenomenon and its consequences are causing many disadvantages for patients with SSc. The current treatment for peripheral vascular lesions are oral vasodilators that sometime not

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effective. To contribute to resolve this problem, we conducted the study **"Efficacy and safety of intravenous iloprost in the treatment of Raynaud phenomenon and digital ulcers in patients with systemic scleroderma".**

2. METHODS

31 patients over 18 years old suffering from SSc was treated iloprost infusion in National Hospital of Dermatology and Venereology from April 2017 to March 2020.

The protocol of iloprost infusion: The course of treatment consists of 2 times with 2 days apart, each time for 5 consecutive days, 6 hours/day. The dose started at 0.5 ng/kg/min and increased by 0.5 ng/kg/min every 30 minutes. The tolerable dose was determined during the first 3 days and maintained in the following days.

Evaluation was done after 2 weeks and included:

Width of ulcer: Grade 1: < 0.2 cm; Grade 2: 0.2 - 0.4cm; Grade 3: > 0.4 cm.

Depth of ulcer: Grade 1: crack; Grade 2: superficial ulceration; Grade 3: deep ulcer.

Raynaud phenomenon: Patients rate by themselves on a VAS scale from 0 to 100.

Laboratory tests was performed at week 0 and week 2.

Record the patient's side effects during treatment.

3. RESULTS

Characteristics of the subjects

Table 1. Characteristics of the subjects

Characteristic			
Gender (n,%)	Female	22	71%
	Male	9	29%
Age of onset		41,3 ± 12,3	Min = 10 Max = 55
Age of patient		50,5 ± 13	Min = 20 Max = 69

Among 31 patients, females predominate, accounted for 71%.

The average age of onset of the disease was 41.3 ± 12.3, the youngest was 10 years old, the oldest was 55 years old.

The average age of patients was 50.5 ± 13 years old, the youngest was 20 years old, the oldest was 69 years old.

The effectiveness of the drug

Raynaud Score Improvement

Table 2. Improvement of Raynaud score

	Week 0 (W0)	Week 2 (W2)	P
Raynaud Score	71,5 ± 11	36,9 ± 17	p < 0,001*

*(*t - test Mcnemar)*

Raynaud score decreased significantly after 2 weeks of treatment (p < 0.001, paired t-test)

The improvement of ulcer lesion

Table 3. Improvement of ulcer lesion

Week		Week 0 (n,%)	Week 2 (n,%)	P
Ulcer depth	Grade 1	25 (25.8)	28 (28.9)	< 0.001*
	Grade 2	52 (53.6)	68 (70.1)	
	Grade 3	20 (20.6)	1 (1)	
Ulcer width	Grade 1	24 (24.7)	37 (38.1)	< 0.001**
	Grade 2	39 (40.2)	47 (48.5)	
	Grade 3	34 (35.1)	13 (13.4)	
Total		97	97	

*(*Chi-square ** chi-square McNemar Bowker)*

The ulcer depth improved markedly after 2 weeks of intervention, the rate of deep ulcers decreased from 20.6% to 1%, significant difference with p < 0.001.

The ulcer width improved markedly after 2 weeks of intervention, the rate of grade 3 decreased from 35.1% to 13.4%, significant difference with p < 0.001.

The safety of the drug

3.1. Change in laboratory test

Table 4. Change in laboratory test

		Baseline	After treament	P
White blood cell	WBC < 4 G/L	0/31	0/29	
	Mean	9.2 ± 3.5	9.4 ± 3.6	0.782*
Neutrophil	Neut < 1.5 G/L	0/31	0/29	
	Mean	6.4 ± 3.1	6.4 ± 2.8	0.962*
Red blood cell	Mean	4.47 ± 0.68	4.43 ± 0.54	0.55***
Hemoglobin	Hb < 130	16/31	12/29	0.453**
	Mean	131.1 ± 17.9	130 ± 13.2	0.7*
Platelet	Plat < 150	0/31	1/29	
	Mean	314.4 ± 99.4	298.0 ± 92.1	0.093*
Ure	> 8.3 mmol/L	0/31	0/30	
	Mean	4.4 ± 1.3	4.4 ± 1.2	0.763*
Creatinin	> 106 µmol/L	0/31	0/30	
	Mean	65.6 ± 10.5	63.3 ± 10.8	0.264*
SGOT	> 80 U/L	1/31	0/30	
	Mean	26.6 ± 15.3	22.0 ± 7.6	0.102*
SGPT	> 80 U/L	1/31	1/30	0.5**
	Mean	20.4 ± 16.6	20.8 ± 19.2	0.918*

*(*McNemar t - test **McNemar Chi-squared test ***paired t-test)*

Only 1 case showed thrombocytopenia below 150 G/l after treatment. There was no statistically significant change in white and red blood cell compared to baseline.

There were no significant changes in renal function and liver enzymes after 2 weeks treatment.

3.2. Change in vital signs

Table 5. Change in vital signs

		Baseline	After treatment	P
Systolic blood pressure	> 140 mmHg	0/31	0/31	
	Mean	110.2 ± 10.8	110.3 ± 9.1	0.932*
Diastolic blood pressure	> 90 mmHg	0/31	0/31	
	Mean	69.7 ± 8.0	68,1 ± 6,5	0.258*
Pulse	> 100 t/m	1/31	1/31	0.5**
	Mean	86.7 ± 6.1	88.2 ± 5.3	0.141*

There was no change in pulse and blood pressure.

3.3.3. Side effects during iloprost infusion

Table 6. Side effects during iloprost infusion

	n	%
No side effect	19	61.3
	7	22.6
Headache	3	9.7
Flush	2	6.5
Infusion side reaction	2	6.5
	5	16.1
Headache + Nausea/vomiting	2	6.5
Headache + Hypotension	2	6.5
Headache + Flush	1	3.2

The rate of patients having side effects when infusion accounted for 38.7%, mainly headache.

3.4. Tolerated dose

Table 10. Grade of tolerated dose

Grade	n	%
Grade 2	1	3.2
Grade 3	11	35.5
Grade 4	19	61.3

The majority of patients tolerated the drug at the maximum infusion rate (level 4), accounted for 61.3%. None of the patients required a level 1 infusion.

4. DISCUSSION

4.1. Effectiveness of intravenous iloprost in the treatment of Raynaud's phenomenon and digital ulcers in patients with SSc

4.1.1. Improvement in Raynaud's score

In SSc, vessels are damaged in almost organs such as the heart, kidneys, lungs, muscles, skin and manifested as Raynaud's phenomenon, digital ulcers, vasodilation, myocardial disorders, renal fibrosis, pulmonary hypertension [4]. The VAS scale for patients to self-assess Raynaud's score showed that after 2 weeks of intravenous iloprost, Raynaud's score decreased significantly from 71.5 ± 11 to 36.9 ± 17 ($p < 0.001$). Many researches around the world also showed a good effect of iloprost on Raynaud's phenomenon in patients with SSc. Bettoni et al. (2002) treated 28 SSc patients who had peripheral vascular lesions with the 6h/day infusion regimen at the highest tolerated dose (mean 2.26 ng/kg/min) for 5 consecutive days then maintenance infusion every 3 weeks, the patient's VAS decreased from 10 to 5 (4.0 - 6.75), $p < 0.001$ [5]. Casigliani Rabl et al treated 73 SSc patients with digital ulcers using iloporst (2012) dose 0.5 ng/kg/min - 1.5 ng/kg/min, they found that Raynaud score according to VAS decreased from 7.3 to 6 with $p = 0.025$ [6]. In addition, there are many studies on iloprost in SSc patients have shown the effectiveness in reducing the frequency, duration, and severity of Raynaud's phenomenon as studied by Fredrick M.Wigley (1992) [7]; G. Milio (2006) [4]; Annegret Kawald (2008) [8]. Several other studies have also suggested the effect of iloprost on Raynaud's phenomenon by significantly increasing the temperature, oxygen saturation of the tip [9], the blood flow velocity in fingers lasting up to 4-9 weeks after intravenous iloprost [10].

4.1.2. Improvement in digital ulcers

In our study, 31 patients with digital ulcers treated with intravenous iloprost according to the protocol were evaluated their ulcers after 2 weeks on width and depth of the ulcer. The results showed ulcer lesions were improved in both width and depth. The rate of deep ulcers decreased sharply from 20.6% to 1% ($p < 0.001$). The rate of grade 3 ulcers decreased from 35.1% to 13.4% ($p < 0.001$). The regeneration of ulcers is

achieved quickly at the end of the 2-week regimen and makes a great improvement in the patient's health. The results also showed that, after 2 weeks, the number of ulcers did not change, which is reasonable because the completely epidermal regeneration time usually takes at least 4 weeks.

Many studies manifested evidence of the effectiveness of iloprost in the treatment digital ulcers in SSc patients. In 1991, Torley et al. found that after 8 weeks of treatment with intravenous iloprost, the number of ulcers was reduced to 44% at 0.5 ng/kg/min and 39% at 2 ng/kg/min [11]. Comparing the efficacy of iloprost versus placebo in patients with systemic scleroderma, Wigley et al. found that after 10 weeks, the percentage of patients with complete ulcer healing was 86% and 0%, respectively [7]. A study by Bettoni et al in 2002 on 22 SSc patients with digital ulcers treated iloprost with an average dose 2.26 ng/kg/min x 6 hours/day for 5 consecutive days then repeated 1 day in every 3 weeks found that 19/21 (90%) patients had complete ulcer healing. A study by Colaci et al in 2016 on 50 SSc patients who treated iloprost for more than 2 years with an once a month regimen 0.8-1ng/kg/min found good results in controlling peripheral vessel lesions. In 31/50 patients with digital ulcers, 22 patients (71%) had complete ulcer healing, 9 patients had chronic or recurrent ulcers. Among 19/50 patients without ulcer, only 1 patient developed ulcer after 2 years [12]. Thus, iloprost not only helps in treatment but also is a method of preventing digital ulcers - one of the common injuries and greatly affects patient's health/quality of life. The research by Rosario Foti (2017) also made the same conclusion when using iloprost and followed up for 7.1 ± 2.9 years and found that the rate of patients with digital ulcers decreased from 42.6% to 11.8%. , no patients developed new ulcers [13].

In addition, some studies have also suggested that using cycle iloprost for long-term will help stabilizing cardiac/lung functions [13], [14]; improving mouth opening [15]; positive effects on skin sclerosis and gastrointestinal symptoms [9]; limiting and delaying the occurrence of life-threatening organ damages [16].

4.2. Safety of intravenous iloprost in the treatment of Raynaud's phenomenon and digital ulcers in patients with SSc

4.2.1. Change in laboratory test

In our study, no significant changes were observed in either red blood cells, white blood cells and platelets. In this study, leukocytes had a slightly increase after treatment ($p = 0.782$). This has also been shown in the study of Helen I Torley et al. (1991) on 55 SSc patients treated iloprost, the average white blood cell count increased from 6.7 G/L to 7.5 G/L [11]. The action of iloprost on platelet is to inhibit platelet aggregation through increased intracellular cAMP levels, which may lead to increasing platelet count [17]. The results from research of Belch J J F (1985) and Helen I Torley [11] support this hypothesis. However, our study was not consistent with the above statement, the platelet count decreased slightly after treatment and there was 1 case of decreasing platelet under normal level.

After iloprost treatment, no changes in renal function and liver enzymes were detected. Several studies have also evaluated the affects of iloprost and have shown a positive effect on renal function. Yasin Ay et al conducted iloprost treatment on 48 patients with severe limb ischemia and found that the group of patients with chronic renal failure significantly reduced the level of urea/creatinine ($p < 0.05$) and significantly increased the glomerular filtration rate ($p < 0.05$) (2013) [18]. Angeli P et al.

(1998) studied 10 patients receiving iloprost at a dose of 1ng/kg/min and 7 patients with a dose of 2ng/kg/min found renal plasma flow, Na secretion increased and Na reabsorption decreased at higher doses ($p < 0.025$) [19]. The drug also has a good effect on the capillary liver network, especially after liver transplant cases [20].

4.2.2. Change in vital signs

Before and after infusion of iloprost, the patient's main vital signs such as pulse, temperature, and blood pressure did not change. These indicators were measured before starting the drug and after the patient had finished treatment in a resting state. The hypotensive effect of iloprost is usually observed only during infusion and returns to stability when the infusion rate is reduced.

4.2.3. Side effects of iloprost infusion

In this study, we found that the rate of patients with side effects accounted for 38.7% such as headache, hypotension, flushing, nausea/vomiting, infusion site reactions. Side effects during infusion are seen when the patient is transfused at high rates, returning to stability when the rate is adjusted down. There were 2 patients who had a reaction at the infusion site such as a red macule, itching and slight burning, the diameter of the red macule is usually about 5 - 6 cm. For this reaction, we did not reduce the infusion rate but interrupt for 10 - 15 minutes or change the location, the macule then usually disappear and do not reappear in following infusions. Our results are similar to the studies of many authors such as Casigliani (2012) [6], Bettoni et al. (2001) [5], Helen I Torley et al. (1990) [11]. All common side effects of iloprost are related to the drug's vasolidating effect, there have been no cases caused by coagulation disorders.

4.2.4. The drug tolerance

The efficacy of intravenous iloprost in treating Raynaud's syndrome and digital ulceration in SSc patients was better in the standard dose group (2 ng/kg/min) than in the low dose (0.5 ng/kg/min) group is result of many studies [9], [11]. However, this difference is not large and can be explained by the effect of iloprost on peripheral vascular injury not only by vasodilating effect but also by increasing fibrinolysis, inhibiting platelet aggregation, reducing leukocyte aggregation. In order to achieve the standard dose and minimize discomfort during the infusion, a regimen with gradually increases the rate of transfusion is recommended. In this study, 31 patients were given the same regimen of iloprost infusion 6 hours/day for 10 days 2 days apart with an increasing rate every 30 minutes from 0.5-1 - 1.5-2 ng/kg/min and measure tolerability in the first 3 days. The results showed that 19 patients (61.3%) tolerated the drug at the maximum rate (level 4), 11 patients (35.5%) tolerated the drug at level 3, 1 patient tolerated the drug at level 2, no patients had to take drugs at level 1. Our results are similar to some other authors. Rademaker et al. used gradually increasing dose of iloprost for 23 SSc patients found that 13 patients tolerated drug at level 4, 10 patients tolerated at level 3 (1989) [21]. Bellando-Randone's research on to 81 SSc patients who were treated iloprost found that side effects appeared to increase with infusion rate, all patients tolerated the drug when the infusion was less than 10ml/h (equivalent to 0.5 ng/kg/min). 2018) [22].

5. CONCLUSION

Intravenous iloprost is a safe and effective treatment for Raynaud's phenomenon and digital ulcers in patients with systemic scleroderma.

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