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ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

Iloprost as Adjuvant to Sildenafil in Connective Tissue Disease-Associated Pulmonary Hypertension

Bağ Dokusu Hastalığı ile İlişkili Pulmoner Hipertansiyonda Sildenafil'e Adjuvan Olarak İloprost

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Abstract

OBJECTIVE: To evaluate the clinical effects of adding inhaled iloprost to sildenafil for the treatment of patients with connective tissue disease (CTD)-associated PAH.

MATERIAL AND METHODS: Consecutive patients with connective tissue disease-associated PAH who received sildenafil for at least three months were enrolled and started on iloprost inhalation. At the end of six months, the patients were reassessed for changes in their New York Heart Association (NYHA) functional class, six-minute walk distance (6MWD), plasma brain natriuretic peptide (BNP) level, and their quality of life as assessed using the short form 36 (SF-36) health survey questionnaire.

RESULTS: The study included 27 patients with a mean age of 46.3±14.5 years. Scleroderma was most common primary diagnosis in 37% of cases. In the 23 patients who completed the study, NYHA class improved from 2.9±0.5 to 2.1±0.5 (p=0.027). Their 6MWD increased by 31% (262.1±126.2 m vs. 342.9±110.6 m; p<0.001). Post-exercise oxygen saturation increased from 85.9±9.1% to 90.4±5.9% (p<0.0001). The SF-36 score for general health and role limitation due to physical problems improved significantly. No difference in BNP was noted.

CONCLUSION: The addition of iloprost to sildenafil for treatment of connective tissue disease-associated PAH resulted in significant improvement in NHYA functional class, 6MWD and quality of life.

KEY WORDS: Iloprost, pulmonary hypertension, sildenafil

Özet

AMAÇ: Bağ dokusu hastalığı (BDH) ile ilişkili PAH'lı hastaların tedavisi için sildenafil'e, inhale iloprost eklemenin klinik etkilerini değerlendirmek.

GEREÇ VE YÖNTEMLER: En az 3 aydır sildenafil alan BDH ile ilişkili PAH'lı ardışık hastalar kaydedildi ve iloprost inhalasyonuna başlatıldı. Altı ayın sonunda, hastalar New York Kalp Derneği (NYKD) fonksiyonel sınıfları, 6-dakika yürüme mesafesi (6DYM), beyin natriüretik peptidi (BNP) ve yaşam kalitesi değişiklikleri yönünden kısa form-36 (KF-36) sağlık sürvey anketi kullanılarak tekrar değerlendirildi.

BULGULAR: Çalışma ortalama yaşı 46,3 (14,5) yıl olan 27 hastayı kapsadı. Skleroderma hastaların %37'sinde birincil tanıydı. Çalışmayı tamamlayan 23 hastada NYHA sınıfı 2,9'dan (0,5) 2,1'e (0,5) düzeldi (p=0,027). Bu hastaların 6DYM'leri %31'lik artış gösterdi (262,1±126,2 m'ye karşılık 342,9±110,6 m p<0,001). Egzersiz sonrası oksijen satürasyonu %85,9±%9,1 %90,4±%5,9 yükseldi (p<0,0001). Genel sağlık ve fiziksel sağlık nedeniyle rol limitasyonu açısından KF-36 skoru anlamlı bir şekilde düzeldi. BNP'de bir fark kaydedilmedi.

SONUÇ: BDH ile ilişkili PAH'lı hastalarda sildenafil'e ardışık şekilde iloprost eklenmesi NHYA fonksiyonel sınıfta, 6DYM'de ve yaşam kalitesinde anlamlı düzelme ile sonuçlandı.

ANAHTAR SÖZCÜKLER: İloprost, pulmoner hipertansiyon, sildenafil

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INTRODUCTION

Pulmonary hypertension (PH) is a serious condition with significant morbidity and mortality [1,2]. The disorder can be classified as pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease, pulmonary hypertension due to left heart disease, lung diseases and hypoxia, chronic pulmonary thromboembolism and pulmonary hypertension with unclear mechanisms [3]. Better understanding of the pathophysiology of PAH has led to the introduction of three main classes of drugs that target vasoconstriction, vascular remodelling and in situ thrombosis [4-6]. These include phosphodiesterase inhibitors, endothelin receptor blockers and prostanoids [1,7]. However, as the course of PAH is known to be progressive, some patients may not reach their treatment goals with monotherapy and therefore require the addition of other therapeutic agents [8-11]. Although various combination regimens have been investigated, the majority of patients in previous studies were those with idiopathic pulmonary arterial hypertension (IPAH), and to date, no study has reported the clinical effects and changes in quality of life following the addition of inhaled iloprost for patients with connective tissue disease (CTD)-associated PAH who were on existing sildenafil therapy [12-14].

The aim of this study was to evaluate the changes in NYHA functional class, six-minute walk distance (6MWD) and quality of life after six months of combination therapy with iloprost and sildenafil in patients with CTD-associated PAH.

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MATERIAL AND METHODS

Patients with CTD-associated PAH who were referred to the pulmonary service at King Khalid University Hospital, Riyadh, Saudi Arabia between November 2009 and June 2011 were recruited for this study. PAH was defined as a systolic pulmonary artery pressure (SPAP) >50 mmHg, a tricuspid regurgitation velocity >3.4 m/sec measured by Doppler echocardiography and a mean pulmonary artery pressure (mPAP) defined by right heart catheterisation of ≥25 mmHg at rest [15,16]. Patients with left heart disease (pulmonary capillary wedge pressure, PCWP >15 mmHg), life-threatening ventricular arrhythmia, uncontrolled systemic arterial hypertension, chronic venous thromboembolic disease or interstitial lung disease revealed by a high-resolution CT scan of the chest were excluded from the study.

All patients had been treated with 25 mg sildenafil three times daily for at least three months prior to enrolment. Other general treatments were allowed, with the exception of prostanoids and endothelin receptor antagonists. Calcium channel blockers started at least two months prior to the study were allowed to be continued at the same dose. All patients were symptomatic and met the criteria of NYHA class 2, 3 or 4.

The study was approved by the Institutional Review Board and Ethics Committee of the King Saud University College of Medicine, and prior written informed consent was obtained from all patients. Eligible patients underwent a baseline assessment that included medical history, physical examination and determination of NYHA functional classification. Pulmonary function tests and a six-minute walk test were performed in accordance with the American Thoracic Society guidelines [17]. Arterial blood gases and plasma BNP level were measured before and after the initiation of iloprost therapy. SPAP was calculated by Doppler echocardiography from the peak velocity of the tricuspid regurgitant jet and the inferior vena cava collapsibility using the simplified Bernoulli equation. If the tricuspid regurgitant jet signal was not adequate, SPAP was calculated using the Meehan formula [18]. Right heart catheterisation was performed to measure mPAP, PCWP, pulmonary vascular resistance (PVR), cardiac output (CO), and the cardiac index (CI). Health-Related Quality of Life (HRQOL) was assessed using the self-administered, validated Arabic version of the SF-36 questionnaire [19-21].

Patients were instructed to inhale 20 mcg iloprost six times daily with a break during sleep. All patients used an Omron NE-U22 MicroAir ultrasonic nebuliser (Omron Corporation, Kyoto, Japan). At the end of the study period, patients who completed six months of treatment were reassessed for their NYHA class, BNP and HRQOL. The same respiratory technician measured the baseline and end-of-study 6MWD.

Statistical Analysis

The collected data are presented as the mean±standard deviation or as percentages. Statistical analysis was carried out using Predictive Analysis Software, version 18 (PASW, IBM, Chicago, Illinois). Comparison of the mean values of the clinical measurements before and after iloprost therapy was performed using a paired t-test, and $p<0.05$ was considered statistically significant.

Table 1. Baseline characteristics of intent-to-treat population

Characteristics	n=27
Age (years)	46.3±14.5
BMI (kg/m²)	34.4±12.5
Gender	
Male	3 (11.1%)
Female	24 (88.9%)
Underlying connective tissue disease	
Scleroderma - diffuse	6 (22.2%)
Scleroderma - limited	4 (14.8%)
SLE	8 (29.6%)
MCTD	6 (22.2%)
RA	3 (11.1%)
Medications	
Calcium channel blockers	6 (22.2%)
Anti-coagulants	8 (29.6%)
Oxygen therapy	7 (25.9%)
6MWD (meters)	245.1±127
NYHA class	
II	6 (22.2%)
III	16 (66.6%)
IV	5 (18.5%)
BNP (pg/mL)	58.3±55.4
DLCO (% predicted)	36.1±16.9
FVC (% predicted)	80.7±6.9
PaO_2 (mmHg)	68.5±24.3
SPAP (mmHg)	64.4±21.2
Haemodynamic parameters (n=26)	
mPAP (mmHg)	35.6±11.7
PVR (wu)	4.7±2.3
CO (L/min)	5.0±1.0
CI (L/min/M²)	2.6±0.5
RAP (mmHg)	8.6±4.1
PCWP	10.9±4.0

Data are presented as the mean±SD or as the number of cases with characteristics/total number of cases (percentage). Abbreviations: SLE, Systemic Lupus Erythematosus; MCTD, Mixed Connective Tissue Disease; RA, Rheumatoid Arthritis; 6MWD, 6 Minute Walk Distance; BNP, Brain Natriuretic Peptide; DLCO, Diffusion Lung Capacity; mPAP, Mean Pulmonary Arterial Pressure; PVR, Pulmonary Vascular Resistance; CO, Cardiac Output; CI, Cardiac Index; RAP, Right Atrial Pressure; PCWP, Pulmonary Capillary Wedge Pressure

RESULTS

The study included 27 intention-to-treat patients with a mean age of 46.3±14.5 years. The majority were female (88.9%). The underlying CTDs (Table 1) included diffuse or limited scleroderma (10 patients), systemic lupus erythematosus (SLE; 8 patients), mixed connective tissue disease (MCTD; 6 patients), and rheumatoid arthritis (RA; 3 patients). Eight patients with scleroderma were hypertensive and three patients had renal impairment (creatinine clearance <50 mL/

min). Haemodynamic measurements were obtained at baseline from right heart catheterisation in 26 patients and were consistent with pre-capillary PH (mean PAP 35.6±11.7 mmHg, mean PCWP 10.9±4.0 mmHg). The mean forced vital capacity (FVC) obtained by spirometry was 80.7% of the predicted value (Table 1).

Four out of the 27 patients enrolled did not complete the study. The reasons for dropping out of the trial were as follows: one patient with scleroderma refused right heart catheterisation; one patient with SLE stopped iloprost due to intractable cough and dyspnoea; one patient with RA stopped due to flushing, severe fatigue and dizziness; and one patient with MCTD died two months after enrolment. The remaining 23 patients who completed the six-month study period, showed a statistically significant improvement in 6MWD compared to baseline (262.1 m vs. 342.9 m; p<0.001) and in NYHA class (p=0.027) (Table 2). The mean increase in walking distance was 80.8 m (31% greater than baseline). Oxygen saturation at the end of the exercise increased significantly from 85.9% to 90.4% (p<0.0001). The BNP measurement did not significantly differ between baseline and six months (Table 2). The overall SF-36 score was higher after treatment with iloprost compared to baseline (52.8 vs. 44.31; p=0.04). The score for general health and role limitation due to physical problems improved significantly after adding iloprost (Table 3).

DISCUSSION

In this study, we demonstrated a favourable clinical response following the addition of inhaled iloprost to pre-existing sildenafil therapy in patients with CTD-associated PAH. Patients with PAH, like those studied herein, have been relatively under-represented in studies that have assessed different therapeutic agents, and they are known to have generally worse outcomes compared to patients with IPAH [22-24].

There was significant improvement in the NYHA functional class and the 6MWD six months after administering iloprost to patients who were already on existing sildenafil therapy. The additive benefit of inhaled iloprost might be attributed to its selective vasodilatory action on the pulmonary circulation leading to improvement in ventilation perfusion mismatch, in addition to its inhibitory effect on platelet aggregation and smooth muscle proliferation [25,26]. Previous studies on the acute haemodynamic effects of the concomitant use of sildenafil and inhaled iloprost have demonstrated a significantly lower mean PAP compared to either drug alone [13,27]. This could be due to the additional pulmonary vasodilatory properties of sildenafil, in addition to its interaction with iloprost, that leads to an increase in the half-life of iloprost. Furthermore, the use of oral sildenafil as an adjunct therapy for patients who deteriorate despite ongoing treatment with inhaled iloprost has been shown to improve exercise capacity and pulmonary haemodynamics [28].

Table 2. Comparison of clinical endpoints before and after iloprost therapy

Clinical Parameters	Before iloprost (n=23)	After iloprost (n=23)	p value
6MWD (metres)	262.1±126.2	342.9±110.6	<0.0001
O_2 sat after exercise (%)	85.9±9.1	90.4±5.9	<0.0001
NYHA Class	2.9±0.5	2.1±0.5	0.027
BNP (pg/mL)	58.4±54.4	54.9±68.5	0.790
PaO_2 (mmHg)	71.8±26.8	69.4±14.4	0.720
$PaCO_2$ (mmHg)	42.3±10.8	38.1±6.3	0.060
DLCO (% predicted)	42.9±16.6	43.2±17.8	0.950

Data are presented as the mean ± SD. See Table 1 legend for the abbreviations

Table 3. SF-36 questionnaire results before and after iloprost therapy

Item*	Before iloprost (n=23)	After iloprost (n=23)	p value
Physical functioning	43.85±25.9	49.62±22.5	0.48
Role limitation due to PH	39.23±30.7	61.54±28.2	0.009
Role limitation due to EP	43.59±41.7	60.38±34.34	0.12
Fatigue	35.38±13.4	39.62±24.3	0.51
Emotional well-being	57.85±27.0	59.08±23.7	0.79
Social functioning	52.04±30.1	55.00±24.8	0.57
Pain	42.58±17.0	49.62±27.9	0.35
General health	40.00±15.0	47.69±12.18	0.03
Total score	44.31±14.5	52.8±16.79	0.04

Data are presented as the mean ± SD; * all items are scored out of 100. Legend: PH: Physical Problems, EP: Emotional Problems

Several parameters have been proposed in the literature to assess the severity of PH and follow the clinical response in patients. In this study, there was significant improvement in the NYHA functional class, a parameter that is considered a valuable prognostic factor in PH and has been found to correlate with changes in haemodynamics [29]. Similarly, there was a significant increase in the 6MWD and post-exercise oxygen saturation after starting iloprost. Previous studies have shown a strong correlation between changes in the 6MWD and patient clinical and haemodynamic responses to treatment [30,31]. Therefore, it is considered an important treatment goal that guides clinicians when making therapeutic decisions, particularly before the initiation of combination therapy [9].

The HRQOL showed significant improvement after the addition of iloprost. This was more evident in the patients' perception of their general health and role limitation due to physical health. This subjective measure of well-being is thought to parallel improvement in respiratory symptoms and is often used to complement other clinical endpoints [19,21]. BNP, a cardiac hormone secreted from both ventricles in response to volume and pressure overload, has been shown to correlate with changes in pulmonary haemodynamics, right ventricular dysfunction and functional parameters in patients with PH [32]. In our study, BNP levels did not significantly differ before and after treatment. This may be attributed to the milder form of PAH in our patients and their preserved cardiac output.

The limitations of the present study include the small number of patients and the relatively short duration of follow-up. Therefore, further studies with a larger number of patients followed for a longer duration are needed to confirm our results.

In conclusion, the addition of inhaled iloprost to sildenafil for treatment of patients with CTD-associated PAH resulted in improvements in the NHYA functional class, walking distance and post-exercise oxygen saturation during a mean follow-up period of 6 months. In addition, quality of life scores showed an overall improvement, particularly in the domains of general health and role limitation. Our study provides experimental support for this therapeutic strategy in patients with CTD-associated PAH who do not reach their treatment goals with sildenafil therapy alone.

Conflict of Interest
No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of King Saud University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions
Conception - H.O., M.H., N.G.; Design - H.O., E.A., M.A.; Supervision - H.O., M.A., A.A.; Fundings - H.O., N.G.; Materials - H.O., N.G., M.A.; Data Collection and/or Processing - H.O., N.G., E.H.; Analysis and/or Interpretation - H.O., M.H., E.A.; Literature Review - H.O., N.G., A.A.; Writer - H.O.; Critical Review - H.O., M.H., E.A.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

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