Erişkin kadın hastalarda Eisenmenger sendromuna yaklaşım ve pulmoner arteriyel hipertansiyonda spesifik tedavi: Tek merkeze ait klinik sonuçlar ve beş yıllık izlem

Approach to the Eisenmenger syndrome in adult female patients and specific treatment of pulmonary arterial hypertension: Clinical outcomes of a single center and 5 years of follow-up

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ÖZET

Amaç: Eisenmenger sedromu (ES) doğumsal kalp hastalıklarında pulmoner arteriyel hipertansiyonunun (PAH) en ilerlemiş formudur. Bu çalışmada ES'ye yaklaşımı, takip ve PAH'a spesifk tedavinin uygulanma özelliklerini, ortalama 5 yıllık izlem sonrasında klinik sonuçlarını değerlendirmeyi amaçladık. ***Çalışma planı:*** 2008-2013 Mayıs tarihleri arasında takip edilen ES'li kadın hastalar çalışmaya alındı. Hastalar ortalama 5 yıl süre ile izlendi. Klinik bulgular, laboratuvar, BNP düzeyi, transtorasik ekokardiyograf, sağ kalp kateterizasyonu ve 6 dk yürüme testi (6 DYT) bulguları kaydedildi. Spesifk tedavi için hastalara kılavuzların önermiş olduğu şekilde bosentan, iloprost ve sildenafl tek başına ya da kombinasyon şeklinde başlandı. Üç aylık takiplerde mortalite, hastaneye yatma ihtiyacı, ek PAH tedavi ihtiyacı gibi veriler değerlendirildi. ***Bulgular:*** Çalışmaya 12 hasta alındı. Tüm hastalar kadın olup, ortalama yaş 36.5 idi. Prognostik ekokardiyografk veriler olarak, hastaların yüksek pulmoner arter basınç değerleri (109.81±24.94 mmHg) ile alakalı olarak sağ ventrikül duvar kalınlığının ileri düzeyde arttığı, sağ atriyum basınçlarının nispeten yüksek olduğu, hastaların %40'ında ciddi pulmoner yetersizliğin bulunduğu, pulmoner akselerasyon zamanının kısaldığı, sol ve sağ ventriküllere ait miyokardın doku Doppler hızlarının düşük olduğu, sağ atriyum alanı/sol atriyum alanı oranının arttığı (1.35±0.40), sağ ventrikül fraksiyone alan değişim değerinin düşük olduğu saptandı. Ortalama 5 yıllık takip süresinin sonunda toplam 16 olay meydana geldi. Hastaların 8'inde kombinasyon tedavisi gerekti.

Sonuç: Eisenmenger sedromu ciddi morbidite ve mortalite nedeniyle özelleşmiş merkezler tarafından takip edilmesi gereken, çoklu sistemi etkileyen ve spesifk PAH tedavisinden klinik fayda sağlanan hastalık grubudur.

ABSTRACT

Objectives: Eisenmenger syndrome (ES) occurs as the most advanced form of pulmonary arterial hypertension (PAH) in patients with congenital heart disease. In this study, we aimed to evaluate the management of ES patients, follow-up and specific PAH treatment applied, and clinical outcomes during 5 years.

Study design: During the period between May 2008 and 2013 ES female patients were included in the study and followed up for an average of 5 years. Clinical fndings, brain natriuretic peptide levels, transthoracic and right heart catheterization findings, and 6-min walking test distance were recorded. PAH specific treatment including bosentan, iloprost and sildenafil was given to patients according to guidelines. The patients were evaluated with 3 month-intervals as requirement for hospitalization, combination treatment, and mortality. ***Results:*** A total of 12 patients were included in the study. All of the patients were women, the mean age was 36.5. As prognostic echocardiographic data, the patients had high pulmonary artery pressure (109.81±24.94 mmHg) related with increased right ventricular wall thickness, elevated right atrial pressure, severe pulmonary regurgitation in 40%, shortened pulmonary acceleration time, diminished myocardial tissue Doppler velocities of the left and right ventricles, increased right atrium area/ left atrial area ratio (1.35±0.40), lower right ventricular fractional area change. During the follow-up period of 5 years, a total of 16 events occurred. Combination treatment was required in 8 patients.

Conclusion: Eisenmenger syndrome is a multi-system disease and due to high morbidity and mortality risk patients with ES should be followed by specialized centers. PAH specifc treatment improves the disease course and survival of the patients.

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Eisenmenger syndrome (ES) is a multisystem clinical entity characterized by the development of pulmonary hypertension secondary to left –to- right shunt due to preexisting cardiac defect caused by a congenital heart disease (CHD). If this cardiac defect is not closed, pulmonary artery pressure (PAP) rises above systemic blood pressure, and direction of the shunt reverses with the development of right- to- left shunt. ES, emerges as the most advanced form of pulmonary arterial hypertension (PAH). To establish the diagnosis of Eisenmenger syndrome the presence of bidirectional or reversed shunt is required. The most diagnostic finding of these patients is central cyanosis.[13]

Eisenmenger syndrome was firstly defined by Dr. Victor Eisenmenger in 1897, then by Dr. Paul Wood in 1958. Location, and also the size of the defect have been demonstrated to have an important role in the development of this syndrome. In autopsy studies, it has been observed that minimal size of the defect which might cause PAH was 7 mm at aortopulmonary, and 30 mm at the atrial level.[34] Besides, factors including type of the defect, associated noncardiac anomalies, application of corrective interventions should be taken into consideration in the development of PAH.

Since Eisenmenger syndrome involves hematologic, cerebrovascular, cardiovascular, renal, skeletal, rheumatological, and respiratory systems, and bilirubin metabolism, these patients should be closely followed up. Life expectancy, and exercise capacity of the patients with ES decrease when compared with the normal population.[57] Small percentages of patients with ES syndrome rarely reach 30 (75 %), 40 (70 %), and 50 (55 %) years of age. Therefore, diagnosis, treatment, and follow-up of these patients carry greater importance. First, second, and third-year annual survival rates of patients with ES before the introduction of treatment modalities termed as specific to PAH including endothelin antagonists, prostaglandin analogues, sildenafil after establishment of diagnosis were 97, 89, and 77 % , respectively. Moreover acquired cases have a much better prognosis than patients with idiopathic PAH. [8]

Abbreviations:
6 MW 6-minute walk test
BNP Brain-natriuretic peptide
CHD Congenital heart disease
EF Ejection fraction
ES Eisenmenger syndrome
FC Functional capacity
NYHA New York Heart Association
FAB Fulmonary artery pressure
PAH Pulmonary artery hypertension
PVR Pulmonary vascular resistance
RVOTO right ventricular outlfow tract obstruction
RVFAC Right ventricular fractional area change
TAPSE Tricuspid annular plane systolic excursion
VSD ventricular septal defect

Closer, and regular follow-up considerably effects survival rates of the patients with ES.

In this study, we aimed to evaluate approach to ES among the adult female patients, follow-up protocols, PAH-specific treatment pecularities, and clinical outcomes after nearly five years of follow-up.

PATIENTS AND METHOD

Female patients with ES aged ≥ 18 years who were followed up between May 2008, and 2013 were included in the study. This retrospective study was approved by the ethics committee Data about the patients were retrieved from medical files.

Eisenmenger syndrome was detected before admission to our clinic or during our follow-up. ES was determined as systemic increase in PAP, together with cyanosis, and reversed or bidirectional shunt associated with intracardiac pathologies or great vessels which induce a hypoxemic state. Diagnosis was confirmed by right heart catheterization with the guidance of clinical, and echocardiographic findings. Oxygen saturation of < 92 % during rest, and < 87% during exercise were deemed to be significant. Patients with ES related to uncomplicated CHD were included in the study. Patients with complex anomalies were excluded from the study. Patients with pulmonary, liver, connective tissue comorbidities as a cause of their pulmonary hypertension were also excluded from the study. Exercise capacity was evaluated using 6-minute-walk distance (6MWD) test Transcutaneous arterial oxygen saturation was monitored using pulse oxymetre. On a 50-meter- long corridor, 6MWD test was performed in compliance with standards set in guidelines. Functional capacity (FC) was evaluated in compliance with the recommendations of New York Heart Association (NYHA) All patients underwent transthoracic echocardiographic examinations during diagnostic process. Laboratory tests were repeated at the start of the treatment, then one week later, afterwards at 15-day, one-month, finally at 3-month intervals. Data related to mortality, need for hospitalization, and additional PAH treatment were evaluated. In line with the recommendations of the guidelines, the patients did not receive routine anticoagulant treatment. Besides, the patients were interrogated for frequently seen conditions secondary to platelet dysfunction, and factor deficiencies including epistaxis, menorrhagia, hemoptysis, and gingival bleedings.

Conventional treatment (diuretics, digoxine) received by the patients was maintained.. Clinical findings, whole blood cell counts, biochemical parameters, brain-natriuretic peptide (BNP) values, transthoracic echocardiographic findings, and 6MWD test results were reevaluated, and recorded. Since useful outcomes of iron deficiency treatment in patients with ES were previously demonstrated [9] serum iron, and ferritin levels were monitored. Lower serum iron (<30 mcg/L), and ferritin (<50 mcg/L) levels together with decreased transferrin saturation (< 25%) were accepted as iron deficiency, [9] and these patients were treated with once weekly ferro glycine sulfate tablets for the first week, and the subsequent week the patients received 2 iron supplement tablets a week. One month later their iron levels were controlled.

Specific PAH treatment was initiated either by our team or the patient was already receiving PAH treatment at admission. The patients who didn't receive specific treatment were started on bosentan, sildefanil, and iloprost treatment either singly or in combination.[10,11] Bosentan was administered at twice daily doses of 62.5 mg for the first month, and then the dose was increased to twice daily doses of 125 mg. Sildenafil was initiated at a dose of 1 tablet tid. If clinical response was not adequate, then the dose was increased to twice daily doses of 3 tablets. Iloprost treatment was monitored as for side effects, and eligible patients received once daily inhalation dose of nine ampoules. The patients were monitored at the highest dose they could tolerate. During right heart catheterization, closability of the defect was reviewed in consideration of the ratio between systemic, and pulmonary flow rates (QP/QS), and measurements of pulmonary vascular resistance (PVR) even if the diagnosis of ES had been made in another center. Diagnosis of PAH was based on the presence of mean PAP ≥25 mmHg, pulmonary capillary wedge pressure (PCWP) ≤15 mmHg, and PVR >240 dynxsxcm-5. Besides, before initiation of PAH-specific treatment, vasoreactivity was evaluated using adenosine infusion. Patients with complex congenital defects, left ventricular dysfunction with lower left ventricular ejection fraction (EF) (45%), and coronary artery disease were excluded from the study.

Transthoracic echocardiographic evaluation was performed using, Vivid 7 device Vivid 7, (Vingmed, GE) in line with the recommendations of American Association of Echocardiography. From standard views (parasternal long axis, apical two, and three chamber, apical long-axis views) two-dimensional images were obtained.

Left ventricular end-diastolic, and end-systolic volumes (LVEDV, RVESV), and diameters (LVEDD, RVEDD), EF, left (LAD), and right atrial (RAD) diameters and volumes were measured. Left, and right atrial diameters were measured in 4-chamber views. Left, and right atrial areas were measured at the end of systole. Pulmonary artery systolic pressure was estimated by adding tricuspid valve gradient to the right atrial pressure. In the determination of the right atrial pressure, diameter of inferior vena cava, and also respiratory response were evaluated. In the apical 4-chamber view, continuous Doppler US was used to measure the rate of the highest tricuspid regurgitant flow. Using pulsed tissue Doppler US, myocardial velocities were measured in apical 4-chamber views, and at the level of mitral (Me, Ma, Ms), and tricuspid annulus (Te, Ta, Ts) over the right ventricular wall. On pulsed tissue Doppler images, myocardial systolic S waves, and early diastolic, and atrial contractions were evaluated. .[12-15] Right ventricular basal diameter (RVBD) was measured in 4 chamber view at the end of diastole. Right ventricular outflow tract diameter (RVOTD) was measured in parasternal long, and short axis views. Right ventricular fractional area change (RVFAC) was measured in apical 4-chamber view, and calculated using the formula:
End-diastolic area (cm^2)- end-diastolic area (cm^2)/end-diastolic area (cm^2).

Besides right ventricular end-diastolic (RVED), and end-systolic (RVES) volumes were estimated. Measurement of tricuspid valve annular plane systolic excursion (TAPSE) is based on the determination of right ventricular function, and the longitudinal excursion of the annulus during systolic phase as measured with the aid of a cursor placed on anterior tricuspid annulus through apical 4-chamber view using M-mode Doppler US. A TAPSE > 15 mm is considered normal. Thickness of the right ventricular wall was measured in subcostal window using M-mode method. Pulmonary acceleration time (PAT), and ejection time (EJT) were estimated over pulmonary valve using pulsed Doppler US. The severity of pulmonary insufficiency (PI) was determined in patients with PI. Diastolic pulmonary artery pressure (PAPd) was calculated based on flow rates detected in patients with PI. Some of cardiac catheterization findings including PVR, systemic vascular resistance (SVR),], and QS were recorded.

Clinical deterioration was evaluated in consideration of the need for hospitalization because of PAH, a 15 % shorter 6-minute walk distance determined at least at two –month intervals, concomitant higher BNP values, worsened functional capacity, and findings of right heart failure . The patients were also evaluated as for underlying causal non-cardiac pathologies (i.e. infection, anemia etc). The patients without additional problems who required treatment, were switched to dual, and triple

combination treatment protocols.

Statistical analysis

Statistical analyses were performed using "SPSS for Windows v. 16" program. Continuous variables were expressed as mean ± SD, and categorical variables were indicated as percentages (%). Because of scarce number of patients in our study, changes in parametres after baseline, and termination of follow-up period were evaluated using a non-parametric test (Mann-Whitney-U test). $P < 0.05$ were accepted as the level of statistical significance.

RESULTS

A total of 12 female patients with a median age of 36.5 years were included in the study. Clinical characteristics, and laboratory parameters of the patients are demonstrated in Table 1.The most frequent symptom in patients was dyspnea, and in the evaluation of functional capacity the patients were in NHYA functional class III (41.6 %). Four patients had used warfarin previously. Treatment was discontinued in 2 patients because of hemoptysis. However, the other 2 patients because of the presence of hyperviscosity symptoms, and lack of any history of bleeding, anticoagulation therapy was maintained under close supervision. All patients demonstrated sinus rhythm, and 95% of them had right axis, right ventricular hypertrophy. The patients also had ventricular septal defects (VSD, n=7), aortopulmonary window (n=1), atrioventricular (AV) canal defect (n=1), patent ductus arteriosus (n=2), and atrial septal defect (ASD, n=1).

The patients were receiving monotherapy (n=4), dual (n=2) or triple (n=3) PAH-specific drug combination therapy (Table 2). Patients who were receiving triple drug combination therapy consisted of advanced age individuals who were followed up for the longest period of time (nearly 10 years). While the youngest patients were mostly receiving monotherapy. Before starting PAH-specific drug therapy, during diagnostic stage, one of the three drug groups were selected based on principles set up by guidelines. Then if deemed necessary, second-, and third –line agents were included in the treatment regiment. The decision-making process for the well-being of the patients were evaluated based on essential criteria including, improvement in FC, 6-minute walk distance of ≥ 500 meters especially in young people, return of BNP levels to normal limits, and absence of any echocardiographic parametre(s) indicating poor prognosis (TAPSE > 15 mm, absence of pericardial effusion).

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Table 1. Clinical and laboratory characteristics

	Patients (n=12)		
	n	%	Mean.±SD
Age (years)	36.50		
Oxygen saturation(%)			80.08±8.39
6-minute walk distance (metre)			431.83±98.00
Bosentan	12		
Sildenafil	4		
Iloprost	6		
Functional class III	5	41.6	
Functional class IV	0	0	
Fe deficiency	5	42	
Medications used			
Digoxine	4	33.3	
Diüretic	5	41.6	
ACEI	2	16.6	
Allopurinol	4	41.6	
Hb (g/dl)			15.62±1.92
Hct (%)			48.20±8.03
Uric acid (mg/dl)			5.35±1.84
Brain antriuretic peptide (pg/ml)			367.83±292.50

ACEI: angiotensin- converting enzyme inhibitor; Hb: Hemoglobin; Hct: Hematocrit

Table 2. Characteristics peculiar to the treatment of patients

Patient	Etiology	Age	Initial treatment	Duration	Add-on therapy	Duration	Add-on therapy	Duration
1	Aortopulmonary window	30	Bosentan	2007-	Iloprost-	2011-		
2	Primum type ASD	**77**	Iloprost	2001-	Sildenafil	2002-	Bosentan	2008-
3	Ventricular septal defect	43	Bosentan	2007-	Sildenafil*	1 month	Iloprost	2009-
4	Ventricular septal defect	**22**	Iloprost	2008-	Bosentan	2009-		
5	Patent ductus arteriosus	25	Bosentan	2007-				
6	Patent ductus arteriosus	43	Iloprost	2001-	Sildenafil	2003-	Bosentan	2008-
7	Ventricular septal defect	57	Bosentan	2007-	Sildenafil*	2009-	Iloprost	2010-
8	Ventricular septal defect	31	Bosentan	2007-				
9	Ventricular septal defect	26	Bosentan	2006-	Iloprost	9 monhs	Sildenafil	2011-
10	AV canal defect	**22**	Bosentan	2011-				
11	Ventricular septal defect	**22**	Bosentan	2012-				
12	Ventricular septal defect	29	iloprost	2008-	Bosentan	2008-		

(Prim: Primum; ASD: Atrial septal defect; AV: Atrioventricular (* sildenafil treatment was discontinued in two patients).

Transthoracic echocardiographic findings of the patients are shown in Table 3. Standard echocardiographic data obtained at the start, and end of the follow-up period were compared. Statistically significant changes were not observed in the diameters, and volumes of the left heart, EF, dimensions of the right heart, and PAP. In patients with PAH, accepted prognostic parameters of echocardiography, and right heart catheterization related to the right heart are shown in Table 4.

At the end of a median follow-up period of 5 years, a total of 16 events without any subsequent mortality occurred (Table 5). In eight patients, requirement for combination therapy arised. Some of the patients required dual (n=5), and triple (n=3) drug therapies. Hemoptysis was observed in two patients. One of the patients was under triple combination treatment, and required hospitalization from time to time due to right heart insufficiency. Another patient was using single drug therapy. This patient was evaluated by the department of chest diseases with respect to the additional abnormality which might induce hemoptysis, and hemoptysis was associated with ES. Concomitant regression of FC, decrease in 6MWD, and increase in BNP level of this patient necessitated conversion to dual drug combination therapy. In four young patients, a complicated disease course was not observed. With three-monthly controls, PAH-specific monotherapies were maintained without any clinical deterioration.

Table 3. Changes in standard echocardiographic data obtained at the beginning, and end of the follow-up period

	At the beginning of the follow-up period	At the end of the follow-up period	*p*
Left ventricular end-diastolic diameter (mm)	41.83±3.68	42.33±3.22	0.888
Left ventricular end-systolic diameter (mm)	25.83±3.35	27.2±2.05	0.098
Left ventricular end-diastolic volume (ml)	79.25±16.32	79.75±14.00	1.000
Left ventricular end-systolic volume (ml)	26.91±6.38	28.33±6.21	0.396
Left ventricular ejection fraction (%)	64.08±3.47	62.66±4.27	0.325
Left atrial diameter (mm)	31.83±5.42	32.58±6.09	0.526
Right atrial diameter (mm)	43.08±9.37	43.25±10.16	0.964
Right ventricular diameter (mm)	41.72±7.77	40.16±7.82	0.610
Pulmonary artery pressure (mmHg)	103.50±29.63	113.87±28.56	0.441

Table 4. Prognostic echocardiographic, and catheterization data of the patients

	Mean.±SD
RVEDV (mi)	88.41±28.88
RVESV (mi)	57.16±24.39
RVFAC (%)	35.16±8.89
RVOTD (mm)	33.90±5.34
RAA (cm^2)	20.58±9.63
LAA (cm^2)	12.83±2.40
RAA/SoAA	1.35±0.40
TAPSE (mm)	16.58±2.60
Me (m/s)	6.83±2.24
Ma (m/s)	5.91±1.78
Ms (m/s)	6.25±1.21
Te (m/s)	8.33±1.92
Ta (m/s)	10.08±2.31
Ts (m/s)	10.16±2.82
PAP (mmHg)	109.81±24.94
PAPd (mmHg)	57.28±11.16
QP/QS	1.04±0.33
PVR (wood U)	28.18±24.63
SVR (wood U)	27.15±14.73
PAT (ms)	91.36±20.06
EJT (ms)	224.1±53.48
Pulmonary insufficiency)	Moderate 25%
	Severe 40%
RVDK (mm)	13.06±2.73
RAB (mmHg)	13.04±2.05

RVEDV: Right ventricular end-diastolic volume; RVESV: Right ventricular end-systolic volume; RVFAC: Right ventricular fractional area change; RVOTD: Right ventricular outflow tract diameter;:RAA: Right atrial area; LAA: Left atrial area; RAA/LAA: Right atrial area / Left atrial area; TAPSE: Tricuspid annular plane systolic excursion; Me: Mitral annular tissue Doppler E wave; Ma: Mitral annular tissue Doppler a wave; Ms: Mitral annular tissue Doppler S wave; Te: Tricuspid annular tissue Doppler E wave; Ta: Tricuspid annular tissue Doppler a wave ; Ts: Tricuspid annular tissue Doppler s wave ı; PAP: Pulmonary artery pressure, PAPd: Diastolic pulmonary artery pressure ; PVR: Pulmonary vascular resistance; SVR: Systemic vascular resistance; PAT Pulmonary acceleration time; EjT: Ejection time; PI: Pulmonary insufficiency .

The patient who was receiving dual combination therapy was hospitalized because of sinus tachycardia, and regression in FC. Echocardiographic evaluation of the patient with BNP level within the upper limit of normal (ULN) did not reveal poor prognostic factors. Right heart catheterization performed because of suddenly developed regression in FC revealed the presence of similar findings. Result of the psychiatric consultation reported as major depression, and panic disorder.

Her medical treatment for her psychiatric disorders was arranged with resultant improvement in her functional capacity Three patients in the advanced age group required rehospitralization with the indication of right heart failure. Three patients also required triple combination treatment, and intercurrent infection deteriorated clinical picture. Besides one of these patients required recurrent phlebotomy procedures. When the clinical status of the patients improved, they were discharged with furosemide therapy at doses of 4 tablets a day. At first month controls after hospital discharge diuretic dose was decreased to one tablet a day.

When compared with the patients who hadn't a complicated course, in the patients who developed cardiovascular complication, decreased oxygen saturation, 6-minute walk distance, RVFAC values, while increased RAAa/LVAa ratio, RVOTO were observed. Any difference between clinical, and echocardiographic parametres was not detected.

As drug –induced side effect, liver enzymes elevated three-fold –still within normal limits- in one patient at one month of her bosentan treatment when twice daily doses of 125 mg were initiated Since the patient was 45 kg, her dose was not increased, and she was maintained at twice daily doses of 62.5 mg. Treatment was discontinued because of serious headache, and orthostatic hypotension. Severe nosebleed in one patient necessitated switching from iloprost to another drug therapy.

Iron deficiency detected in five patients during follow-up period necessitated initiation of iron therapy.

In one patient typical gout episode occurred. Allopurinol therapy was started on patients with uric acid levels higher than 9 mg/dl. Among laboratory parameters, most frequently higher bilirubin, and LDH levels, and thrombocytopenia were encountered. Platelet counts did not drop below 80000/mm^3 in any patient. The patients were followed up by the department of hematology, and any additional abnormality was not detected, while thrombocytemia was associated with ES. The patients periodically underwent abdominal ultrasonographic examinations for the monitorization of possible occurrence of hepatosplenomegaly, and gallbladder stone disease. None of the patients required interventional treatment.

DISCUSSION

As a specialized center for PAH, our center evaluated long-term clinical outcomes of ES for the first time.

Table 5. Clinical events observed in patients

Patient	Etiology	Age	Clinical event
1	Aortic window	30	Hemoptysis
2	Primum type atrial septal defect		Switching to combination treatment
		77	Right heart failure
			Need for hospitalization
3	Ventricular septal defect		Switching to combination treatment
		43	Switching to combination treatment
			Palpitations, Need for hospitalization
4	Ventricular septal defect		Major depression
5	Patent ductus arteriosus	22	Switching to combination treatment
6	Patent ductus arteriosus	25	Clinically uneventful
		43	Switching to combination treatment
			Right heart failure
			Need for hospitalization
			Attacks of gout
7	Ventricular septal defect		Hemoptysis
		57	Switching to combination treatment
			Right heart failure
8	Ventricular septal defect		Need for hospitalization
9	Ventricular septal defect	31	Clinically uneventful
		26	Switching to combination treatment
10	Atrioventricular canal defect	22	Clinically uneventful
11	Ventricular septal defect	22	Clinically uneventful
12	Ventricular septal defect	29	Switching to combination treatment

Because of concomitant serious risks of morbidity, and mortality, ES shortens survival times.[16,17] During an average of 5 years of follow-up of our 12 patients with ES, we detected morbidities related to 16 clinical events, without any incident of death. One can assert that lower mean age of our patients, relatively shorter follow-up periods when compared with anticipated life expectancies, and lower risk patient profile because of inclusion of the cases with simple cardiac anomalies might be held responsible for decreased morbidity rates in our patient population. When prognostic echocardiographic data are considered, extremely thickened right ventricular walls of our patients linked with increased PAP values, relatively higher right atrial pressures, presence of severe PI in 40% of the patients, shortened pulmonary acceleration times, decreased myocardial tissue Doppler velocities of the left, and right ventricles, and reduced right ventricular fractional area change (FAC) will be seen. Though these data are compatible with values observed in patients with serious PAH, improved disease progression of our patients more favourable than anticipated, may be explained by their long-term treatment with PAH-specific therapy.

Since the patients with Eisenmenger syndrome are under risk of bleeding, and especially pulmonary hemorrhagia, and hemoptysis because of thrombocytemia, and deficiency of related hematologic factors, and risk of thrombosis, routine application of anticoagulation in these patients is a controversial issue. Therefore routine use of anticoagulant therapy is not recommended for these patients. In our study, nosebleeds were observed in two patients which resolved spontaneously. Nearly two-fifth of the patients with ES suffer from hemoptysis, and it appears to be responsible for 2/5 of the mortality rates in cases with ES: Hemoptysis in patients with ES develop secondary to pulmonary infarction related to neovascularization, abnormalities of hilar intercostal collateral arteries or thrombotic events. If multiple systemic –pulmonary collaterals are detected, then potential anatomic region can be localized, and embolization can be performed. For life-threatening serious hemoptysis, embolization can be the sole treatment modality.[18-20] On the other hand, especially in female patients with ES, the risk of thrombotic complications increases markedly.[21] For these complications, hypercoagulability, abnormalities, and variations in blood flow have been blamed. Since our study population comprised female patients, pulmonary artery, and its diameter were evaluated in detail during echocardiographic controls, and despite routine anticoagulation we applied, any finding in favour of thrombus was not observed.

During the follow-up period, a total of 8 patients were hospitalized because of clinical manifestations of right heart failure. These patients belonged to an advanced age group, and used only a single agent at the start of the follow-up period. However during the follow-up period, due to regression of functional capacity, shortened 6-minute walk distance, and increase in their BNP levels, they could receive triple combination therapy. In a patient whose functional capacity regressed to FC class IV, prostaglandin therapy was planned, but it could not be administered because of patient's refusal. The patients were discharged after improvement of their functional capacities up to FC class III with treatment.

Even though pulmonary artery hypertension has similar pathophysiologic characteristics with other diseases in the same group, more improved prognosis in ES is associated with right ventricle. Right ventricle can not tolerate acute pressure overload higher than 50-60 mmHg, and in chronic disease states, right ventricle wall thickness increases over 5 mm, and assumes a spherical morphology. With increasing pressure, interventricular septum is deviated to the left assuming a configuration of the letter'D'. If the pressure continues to increase, right ventricle, and tricuspid annulus dilate leading to right heart insufficiency. In ES, right ventricle demonstrates variable features. Priorly, presence of a defect allowing left- to- right shunt protects ventricle from pressure overload. Since both ventricles functions at the level of systemic pressure, right ventricular hypertrophy in ES is defined as fetal phenotype.[3,22-24] This condition is especially important in post-tricuspid defects, and right ventricle is primed for higher pressure states. When compared with other PAH groups, right ventricular dilation demonstrates a milder course, while serious tricuspid, and right ventricular insufficiency emerge at a later stage. Therefore ES is better tolerated. Moceri et al. assigned one point to TAPSE <15 mm, duration of right ventricular systolic/diastolic phases ≥1.5, right atrial area ≥25 cm^2, right atrium/left atrium ≥1.5, and detected a significant correlation between mortality rates, and these above-mentioned criteria in patients with ES.[25]

In their study, other prognostic factors including left ventricular eccentricity index, presence of pericardial effusion, right ventricular performance index were not found to be significant..[25] Van De Bruaene et al.[26] demonstrated that TAPSE reflects right ventricular dysfunction in patients with ES. Mortality indicators in ES have been determined as lower FC, clinical findings of heart failure, history of arrhytmia, increase in right atrial pressure, ECG abnormalities, increased uric acid levels, and iron deficiency.[5,27-30] However Kempny et al.[31] determined that FC was devoid of prognostic value, and 6-minute walk distance, and resting oxygen saturation could predict the course of the disease In our study in accordance with literature findings, we observed that in the patient group which demonstrated cardiovascular complications, 6-minute walk distance, oxygen saturation, and RVFAC values were lower, while diameters of the right ventricles were longer reflecting an advanced stage of the disease.

Reardon et al .[32] investigated the correlation between BNP, and ES, and demonstrated that increases in BNP levels were associated with poor clinical course of the outpatients with ES followed up on an ambulatory basis. They especially detected correlations between baseline BNP values over 140 pg/ml, risk of death, and need for hospitalization. Patients with ES, already have higher than normal BNP values because of severely increased PVR, thickening of subpulmonary ventricular wall, and abnormal compliance. [33] BNP is released from myocardial cells related to left, and right ventricular strain.[34,35] In our patients higher BNP values have been detected, and especially in the evaluation of treatment response BNP levels have been used. Since BNP levels over 140 pg/ml has been associated with risk of mortality, and increased need for hospitalization, in our study routine BNP measurements were made during follow-ups.

When our group was analyzed as for prognostic data, our patients appear to be in the moderate risk group. Besides, we think that long-term PAH-specific treatment, and combination treatment received by substantial number of our patients will exert beneficial effects. All of our patients were using bosentan, while iloprost, and sildenafil were used by 50, and 25 % of our patients, respectively. Many studies have demonstrated improvements in clinical state, and exercise capacity of adult patients with ES under bosentan therapy.

With bosentan therapy significant increases have been observed in functional capacity, and 6-minute-walk distance, without any change in echocardiographic findings and any requirement for hospitalization during 2 years of follow-up .[2,36-39] However Kaya et al.[40] observed improvements in FC, oxygen saturation, and 6MWD, and decrease in systolic PAP in patients with ES. In our study group, 4 patients were under bosertan monotherapy, and any clinical event or adverse effect was not encountered or observed. Yang ve et al demonstrated that [41] in patients with ES, iloprost inhalation was safe, and perfectly tolerable, and improved oxygen saturations of FC. Zhang et al. [42] used sildenafil therapy for 12 months, and detected improvements in oxygen saturation, 6MWD test, PAP, and PVR. As reported in many studies, after inadequate response to bosentan therapy in patients with ES, addition of sildenafil to treatment improved clinical state, tolerance to exercise, and hemodynamic parametres..[36] Besides, in patients who received sildenafil in addition to bosentan, manifestations observed before addition of sildenafil therapy such as increases in BNP levels, decrease in 6MWD values, and regression in FC, resolved after addition of sildenafil. Addition of iloprost to bosentan-sildenafil combination therapy also provided similar clinical benefits.[37,42,43] Dimopoulos et al.[37] followed up their 22 patients with ES for 4 years, and observed that PAH-specific therapy had exerted beneficial effects of on survival rates, and so decreased mortality rates. During 5 years of follow-up, the authors indicated that mortality risk was 23 %, and all patients who received PAH-specific therapy during the follow-up period survived In their longest follow-up study, Diller et al .[44] demonstrated that PAH-specific treatment with a single or multiple drug lasting for 8 years, improved symptoms, and exercise capacity. Consequently, the authors accepted decrease in FC, and 6-minute walk distance as determinative factors for switching to combination therapy. Similarly in our study, decrease in FC, and 6-minute walk distance, and increasing BNP levels were considered as determinative factors for switching to combination therapy. However since in a study by Diller et al. prognostic echocardiographic data were not evaluated, risk characteristics of the patients in the study group can not be interpreted. In our study group, three patients were receiving triple combination therapy, in a study by Diller et al. only one patient received this combination therapy.

In our study, the need for rehospitalization arised for three patients because of the development of right heart failure. These in-patients were evaluated, and comorbidities were excluded. Afterwards, reinforcement of the treatment was decided.

Pregnancy is another important factor influential on survival rates of female patients with Eisenmenger syndrome. During follow-up period, none of our patients became pregnant, and as a contraceptive we recommended use of a barrier method.

For patients with appropriate functional capacities, short-term walking exercises 4-5 days a week have been recommended. During follow-up, compliance to treatment of the patients who could perform recommended exercises improved, and the patients indicated increased levels of their self-confidence.

In conclusion, because of its serious morbidities, and mortalities, ES which affects multiple systems should be followed up by specialized centers. Besides, clinically ES responds to PAH-specific treatment modalities. Closer, and regular follow-up regimens can ensure increased survival time, and more comfortable life for these patients.

Limitations of the study

The most important limitation of the study is scarce number of our patient population Besides, since our study population consisted of only female patients, it does not contain outcomes of the male gender. Another deficiency of our study is lack of any comparison between pre-, and posttreatment values because of non-routine use of established prognostic data including TAPSE, and FAC at the start of the follow-up period. However we think that lack of any statistically significant difference between pre-, and posttreatment routine echocardiographic data will compensate for this information gap.

Conflict of interest: None declared.

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Anahtar sözcükler: Bosentan; Eisenmenger sendromu; ekokardiyograf, Doppler; hipertansiyon, pulmoner; iloprost; sildenafl.

Key vvords: Bosentan; Eisenmenger syndrome; echocardiography, Doppler; hypertension, pulmonary; iloprost; sildenafil.