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The Efficacy of Sacubitril/Valsartan in the Treatment of Peripartum Cardiomyopathy: A Retrospective Analysis of Four Cases

Peripartum Kardiyomiyopati Tedavisinde Sacubitril/Valsartan'ın Etkinliği: Dört Olgunun Retrospektif Analizi

ABSTRACT

Peripartum cardiomyopathy (PPCM) is a rare form of cardiomyopathy that develops in the last months of pregnancy or during the postpartum period and is characterized by a decrease in left ventricular ejection fraction below 45%. The diagnosis and management of PPCM can be difficult because the symptoms of the disease may be confused with normal pregnancy symptoms. This requires physicians to maintain a high level of clinical suspicion. PPCM can be fatal if not correctly diagnosed and treated. In this case series, we describe the clinical course of four PPCM patients treated with sacubitril/valsartan (S/V) in addition to standard therapy. In these patients, S/V therapy was associated with improvements in left ventricular function. By the end of the first month, all patients demonstrated recovery of ejection fraction above 50% and were classified as New York Heart Association (NYHA) class I. These preliminary observations suggest that S/V may represent a potential treatment option for PPCM, although confirmation in larger studies is required. Although data on the use of S/V in PPCM remain limited, our case series provides preliminary insights that warrant further investigation. The management of PPCM requires a multidisciplinary approach, emphasizing the importance of timely intervention. Our observations indicate that S/V could be considered a possible therapeutic option, but confirmation in larger cohorts is needed.

Keywords: Ejection fraction recovery, peripartum cardiomyopathy, sacubitril/valsartan

ÖZET

Peripartum kardiyomiyopati (PPKM), hamileliğin son aylarında veya doğum sonrası dönemde ortaya çıkan, sol ventrikül ejeksiyon fraksiyonunun %45'in altına düşmesiyle karakterize nadir bir kardiyomiyopati türüdür. PPKM'nin tanısı ve yönetimi, hastalığın belirtilerinin normal gebelik semptomlarıyla karışabilmesi nedeniyle zor olabilir. Bu durum, doktorların yüksek bir klinik şüphe düzeyiyle hareket etmesini gerektirir. PPKM, doğru tanı konmadığında ve tedavi edilmediğinde ölümcül olabilir. Bu olgu serisinde, sacubitril/valsartan (S/V) tedavisi uygulanan dört PPKM hastası retrospektif olarak değerlendirilmiştir. Dört hastanın tamamında takip sürecinde sol ventrikül fonksiyonlarında düzelme izlenmiştir. Birinci ayın sonunda, tüm hastalarda ejeksiyon fraksiyonunun %50'nin üzerine çıktığı ve fonksiyonel kapasitenin NYHA sınıf I düzeyine geldiği kaydedilmiştir. Bu gözlemler, S/V'nin PPKM tedavisinde potansiyel bir seçenek olabileceğini düşündürmektedir. PPKM tedavisinde S/V'nin kullanımıyla ilgili literatürde sınırlı sayıda çalışma olmasına rağmen, bu gözlemler ön veriler olarak değerlendirilmeli ve daha geniş serilerde doğrulanmalıdır. PPKM'nin yönetimi, multidisipliner bir yaklaşım gerektirir, vaka serimiz zamanında müdahalenin önemini vurgularken, S/V'nin potansiyel bir tedavi seçeneği olabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Ejeksiyon fraksiyonunun düzelmesi, peripartum kardiyomiyopati, sacubitril/valsartan

CASE REPORT
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Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy characterized by left ventricular ejection fraction (LVEF) < 45%, occurring in late pregnancy or early postpartum in women without prior heart disease.[1-3] Despite its rarity, PPCM can cause significant morbidity and mortality, with Turkish cohorts reporting 15–30% mortality during follow-up.[4] The etiology is multifactorial, including genetic predisposition, myocarditis, oxidative stress, and abnormal prolactin cleavage.[5,6]

Risk factors include advanced maternal age, multiparity, pre-eclampsia, multiple pregnancy, and hypertension.[6] Early diagnosis using echocardiography and natriuretic peptides is crucial, as outcomes are strongly influenced by baseline left ventricular (LV) size and function.[7,8] Bromocriptine has been discussed as a potential adjunct but is not routinely recommended.[9] Sacubitril/valsartan (S/V) improves survival in patients with heart failure with reduced ejection fraction (HFrEF), but evidence in PPCM is limited to small reports.[10]

The objective of this case series is to describe the early clinical course of four PPCM patients treated with sacubitril/valsartan in addition to guideline-directed therapy and to provide hypothesis-generating observations on recovery trajectories.

Case Report

Baseline Characteristics and Clinical Presentation

This case series included four women aged 25 to 33 years, diagnosed with PPCM in the postpartum period between 2017 and 2023. Two patients were primigravidae, and two were multiparous (Table 1). Two patients had a history of pre-eclampsia, and one had pre-existing hypertension (Table 2). All patients presented with symptoms of severe heart failure, including orthopnea and findings consistent with hypervolemia. At admission, three patients were classified as New York Heart Association (NYHA) Functional Class III, while one patient presented in cardiogenic shock and was classified as NYHA Class IV (Table 3).

Diagnostic Evaluation

The diagnosis of PPCM was established according to European Society of Cardiology (ESC) criteria, with echocardiography confirming an LVEF below 45% and elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels in all patients (Table 4). A comprehensive differential diagnosis was performed to exclude other causes of cardiomyopathy. Myocarditis was ruled out based on clinical presentation and cardiac magnetic resonance imaging (MRI) findings. Cardiac MRI was performed after improvement in LVEF because of scheduling constraints and limited early MRI availability at our center. As acknowledged in the Limitations section, the delayed timing of MRI represents a limitation of our retrospective case series. Other conditions, such as idiopathic or familial dilated cardiomyopathy, Takotsubo syndrome, pregnancy-associated myocardial infarction, pulmonary embolism, and Human Immunodeficiency Virus-associated cardiomyopathy, were excluded through detailed medical histories, clinical assessment, and imaging (Table 3). Genetic testing was not performed.

Treatment and In-Hospital Course

Following hemodynamic stabilization (systolic blood pressure [SBP] ≥ 100 mmHg or mean arterial pressure [MAP] ≥ 65 mmHg without intravenous vasoactive agents, heart rate [HR] < 100 bpm, peripheral capillary oxygen saturation [SpO_2] ≥ 94% on room air), all patients were initiated on S/V. Standard heart failure therapies, including beta-blockers and mineralocorticoid receptor antagonists (MRAs), were administered to all patients (Table 1). In accordance with updated guidelines (2021 European Society of Cardiology Heart Failure [ESC HF] and 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America Heart Failure [AHA/ACC/HFSA HF]),[11,12] a sodium–glucose co-transporter-2 inhibitor (SGLT2i) was added to the treatment regimen of the fourth case, who was diagnosed in 2023. The patient presenting with cardiogenic shock required positive inotropic therapy and non-invasive respiratory support. This patient also developed atrial fibrillation on the third day of hospitalization, which was successfully converted to sinus rhythm with medical therapy. The duration of hospitalization ranged from four to seven days (Table 5).

Follow-up and Outcomes

Patients demonstrated rapid clinical and functional improvement. NT-proBNP levels decreased significantly

ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
ESC	European Society of Cardiology
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
PPCM	Peripartum cardiomyopathy
S/V	Sacubitril/valsartan
SGLT2i	Sodium–glucose co-transporter-2 inhibitor

Table 1. Demographic characteristics and medication usage of patients

	Case 1	Case 2	Case 3	Case 4
Age (years)	25	29	26	33
Number of pregnancies	2	1	2	1
Primigravida	–	+	–	+
Multiple pregnancy	–	–	–	+
Cesarean birth	–	–	+	+
Sacubitril/valsartan (S/V)	+	+	+	+
Beta-blocker	+	+	+	+
MRA	+	+	+	+
SGLT2i	–	–	–	+
Ivabradine	–	–	–	+

MRA, Mineralocorticoid receptor antagonist; SGLT2i, Sodium-glucose cotransporter-2 inhibitor.

Table 2. Maternal and pregnancy characteristics

	Case 1	Case 2	Case 3	Case 4
Admission time (postpartum)	20	5	10	5
Gestation period (weeks)	36	38	38	39
Preeclampsia	–	–	+	+
HT	–	+	–	–

HT, Hypertension.

Table 3. Hemodynamic and echocardiographic parameters

	Case 1	Case 2	Case 3	Case 4
Saturation, %	95%	93%	92%	78%
Systolic blood pressure, mmHg	110	100	120	80
Diastolic blood pressure, mmHg	65	70	75	55
Heart rate, bpm	105	110	120	110
NYHA class	3	3	3	4
Inotropic support required	–	–	–	+
Respiratory support required	–	–	–	+
LVEF, %	30	25	25	20
LVEDD, mm	58	55	54	60
LVESD, mm	44	42	41	46

LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter; NYHA, New York Heart Association.

Table 4. Laboratory parameters

	Case 1	Case 2	Case 3	Case 4
Creatinine, mg/dL	0.65	0.58	0.78	0.80
Sodium, mmol/L	141	138	140	135
Potassium, mmol/L	4.1	4.8	4.4	3.9
NT-proBNP, pg/mL	10,000	7,000	5,500	12,000
hs-cTnI, ng/L	5	7	10	70
Hemoglobin, g/dL	11	11.4	11.0	10.5
Platelet count, ×10³/μL	132,000	111,000	180,500	162,300
CRP, mg/L	0.3	0.6	0.4	1.4

CRP, C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 5. Comparison of prognostic parameters over time

	Case 1	Case 2	Case 3	Case 4
NT-proBNP, pg/mL				
1st week	3,000	7,000	5,500	12,000
2nd week	800	650	900	1,200
1st month	100	80	100	90
hs-cTnI, ng/L				
1st week	5	7	10	25
2nd week	10	5	7	15
1st month	10	8	12	12
NYHA class				
1st week	2	2	3	3
2nd week	2	2	2	2
1st month	1	1	1	1
LVEDD, mm				
1st week	58	55	54	60
2nd week	50	52	48	52
1st month	44	45	42	46
LVEF, %				
1st week	35	25	35	25
2nd week	45	40	55	40
1st month	55	50	60	50
Number of hospitalization days	4	4	5	7

LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

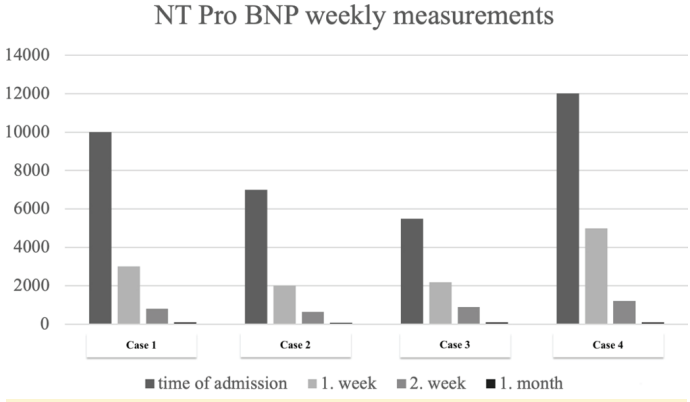


Figure 1. Trajectory of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels from admission to the first month.

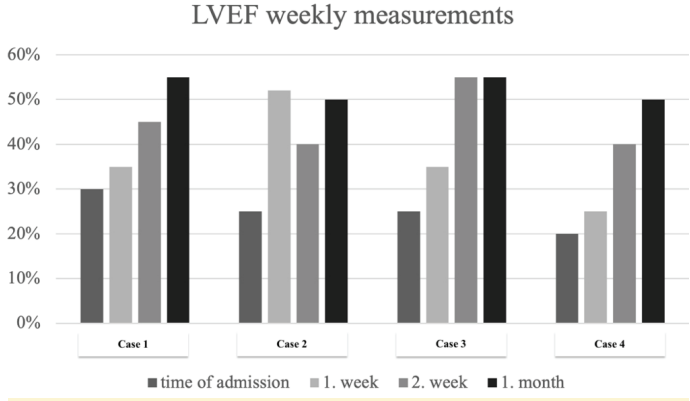


Figure 2. Functional improvement from admission to the first month.

from the first week and normalized in all patients by the first month (Table 5, Figure 1). Descriptively, median LVEF increased from 25.0% at baseline to 52.5% at one month (+27.5 percentage points), median left ventricular end-diastolic diameter decreased from 56.5 mm to 44.5 mm (–12.0 mm), and median NT-proBNP fell from 8,500 pg/mL (interquartile range [IQR]: 6,625–10,500) to 95 pg/mL (IQR: 87.5–100), representing an approximate 99% reduction (Table 5). Concurrently, all patients reported symptomatic improvement and were classified as NYHA class I within the first month (Table 5, Figure 2). During follow-up, no malignant ventricular arrhythmias were observed. One patient had ventricular extrasystoles, but the burden was less than 1% on 24-hour Holter monitoring. All patients tolerated S/V well and completed a 12-month treatment course without any significant adverse events.

Discussion

Peripartum cardiomyopathy is a rare but serious cardiomyopathy with heterogeneous trajectories despite guideline-directed therapy. Our case series describes four women who, in addition to standard heart failure management, received S/V and experienced rapid functional and echocardiographic recovery. Although conclusions are limited by the small sample size and the potential for spontaneous recovery, these observations are noteworthy and hypothesis-generating.[13]

Although bromocriptine has been proposed as an adjunct therapy in PPCM based on mechanistic and limited clinical data, it was not used in our patients due to the absence of robust randomized evidence and safety considerations. Current guidelines emphasize optimization of conventional therapy.[14] Bromocriptine may be considered selectively in patients with severe disease or poor recovery, but larger trials are needed to clarify its role.

Breastfeeding, despite its benefits, poses challenges in PPCM management. The World Health Organization strongly recommends breastfeeding; however, in PPCM patients with NYHA Class III or IV, it is discouraged due to the increased metabolic demands.[15] After being informed about their condition and breastfeeding recommendations, our patients chose to forgo breastfeeding to prioritize optimal medical treatment. For women with severe heart failure, preventing lactation can enhance the efficacy of heart failure medications without posing risks to the infant.

Recovery trajectories in our series appeared faster than those typically reported. Contemporary cohorts and registries—including the ESC EORP registry (European Society of Cardiology EURObservational Research Programme),[8] the 20-year Scottish population study,[16] the Ugandan prospective case–control study,[17] and the multicenter Nigerian cohort[18]—generally report substantial improvements in LVEF and functional status over 3–6 months, with some patients continuing to recover up to 12 months.[19] In contrast, all four of our patients reached an LVEF > 50% and NYHA Class I within one month, and NT-proBNP levels normalized during the same period.

Although such rapid improvement may partially reflect the natural course of PPCM, it is biologically plausible that S/V could contribute to accelerated recovery.[20] Beyond its established benefits in HFrEF, neprilysin inhibition augments natriuretic peptides, leading to improved diuresis, afterload reduction, and reverse remodeling. In PPCM, where maladaptive hemodynamics, neurohormonal activation, and oxidative stress are implicated, early S/V initiation might potentiate rapid unloading and myocardial recovery.[21] Animal models also suggest favorable effects on myocardial fibrosis and remodeling, which could translate to clinical benefit. Nevertheless, causality cannot be inferred from our small, uncontrolled series.

This report is limited by the absence of a control group, the small sample size, delayed MRI timing, and the lack of genetic testing. Accordingly, our findings should be interpreted with caution. However, these cases highlight the need for larger prospective studies and registries evaluating the role of S/V in PPCM. If confirmed, early initiation of S/V may represent a promising adjunct to standard therapy in this high-risk population.

All four cases tolerated S/V well, with no unexpected adverse events. ESC recommends continuing treatment for 12 months post-recovery. We completed the 12-month treatment course, underscoring S/V therapy as a promising approach for managing heart failure in PPCM patients. While S/V may be a potentially life-saving treatment, more data on its safety and efficacy in larger populations are necessary. The broader application of S/V in PPCM treatment hinges on the outcomes of future large-scale clinical trials.

Ethics Committee Approval: Ethics committee approval was obtained from Ordu University Clinical Research Ethics Board (Approval Number: 33, Date: 19.07.2024).

Informed Consent: Patients were informed about the treatment recommended by the guideline and their consent was obtained.

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