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Constrictive Pericarditis: The Effectiveness of Conservative Medical Therapy versus Surgical Pericardectomy

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ABSTRACT

Background: Pericarditis is an uncommon but important disease that can lead to severe symptoms and mortality.
Objectives: This study aimed to evaluate the outcomes of constrictive pericarditis treated by conservative medical therapy in comparison to surgical pericardiectomy.
Methods: In this retrospective study, the records of the patients diagnosed with constrictive pericarditis in Rajaie Cardiovascular, Medical, and Research Center from October 2007 to December 2017 were reviewed. Among the patients, 38 were treated by medical therapy. Thus, 38 patients treated by surgical pericardiectomy were randomly selected to be compared to the medical therapy group. The two groups were compared with regard to the clinical outcomes. Intergroup comparisons were made using chi-square test. In addition, Wilcoxon's signed-rank test was used to compare the patients' New York Heart Association (NYHA) functional classes before and after the treatment. Statistical analysis was performed using IBM SPSS Statistics, version 16.
Results: The mean age of the patients was 51.68 ± 16.37 years in the medical therapy group and 48.43 ± 17.04 years in the surgery group. The main symptoms were dyspnea and edema. Besides, the most common causes were idiopathic (64.4%) and tuberculosis (17.1%) followed by uremia (15.7%) and malignancy (6.5%). Moreover, 84.2% of the patients in the medical therapy group and 97.3% of those in the surgical pericardiectomy group experienced at least one NYHA functional class status, but the difference was not statistically significant. Edema was decreased in 15 out of the 24 patients in the medical therapy group (62.5%) and in 18 out of the 27 patients who had undergone surgical percardiectomy (66.6%), but this difference was not statistically significant (P = 0.74). Furthermore, nine patients in the conservative medical therapy group had been re-hospitalized within the first year of treatment (23.8%), while this measure was found to be six in the surgical pericardiectomy group (15.7%), and the difference was not statistically significant (P = 0.3783). Finally, the perioperative mortality rate was 2.6%, and long-term mortality rate was equal in the two groups (7.8%).
Conclusions: Conservative medical therapy based on the severity and cause of constrictive pericarditis could improve clinical outcomes, especially in patients with transient types of constrictive pericarditis as well as in those who were at a high risk for surgery.

1. Background

Constrictive pericarditis is a chronic inflammatory process involving the pericardium, which leads to fibrotic thickening, scarring, and subsequently calcifications, which could be quite extensive (1). This condition can cause a form of diastolic heart failure by restriction of cardiac filling (2). Several other factors can lead to this condition, as well. In underdeveloped countries and in immunocompromised patients, particularly those infected with Human Immunodeficiency Virus (HIV) or Acquired

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Immunodeficiency Syndrome (AIDS), tuberculous pericarditis has remained the leading cause of constrictive pericarditis (3). In western countries, on the other hand, the most common causes have been reported to be the previous radiation therapy of the chest and previous cardiac surgery although the idiopathic cases are still the most important subgroup (4-6). The main symptoms of this disease include dyspnea on exertion or at rest, edema (lower extremity, ascites, and effusions), pulmonary congestion, and symptoms of low cardiac output (7). Moreover, it is mainly diagnosed via typical clinical signs, such as pulsus paradoxus, jugular venous pulse, pericardial knock, and pericardial rub, as well as by Electrocardiogram (ECG) abnormalities. Non-invasive imaging techniques, such as transthoracic and transoesophageal echocardiography, have been used for diagnosis of constrictive pericarditis. Recently, however, cardiac Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have become the gold standard for diagnosis (6, 8). In addition, cardiac catheterization has been reserved only for patients with suspected diagnoses (9).

Treatment of constrictive pericarditis is based on the severity of symptoms and duration of the disease (2) and consists of medical and surgical treatments. Medical therapy can be useful in patients with specific pericarditis (i.e., tuberculous pericarditis). In this context, anti-tuberculosis antibiotics may significantly reduce the risk of constriction from more than 80% to 10 - 20% (10) as well as transient constriction that occurs in 10 - 20% of cases as a transient phenomenon during the resolution of pericarditis (11). Although constriction is transient or reversible only in a minority of patients with constrictive pericarditis, this finding is particularly important for clinical management, preventing the early indiscriminate use of surgery (11). Medical therapy is supportive and aims at controlling the symptoms of congestion in advanced cases and when surgery is contraindicated or is accompanied with a high risk (12). Otherwise, surgical pericardiectomy is the treatment of choice, which can reduce the patients' symptoms (6, 13, 14).

2. Objectives

The present study aims at comparison of the clinical symptoms and mortality of the patients diagnosed with constrictive pericarditis treated by conservative medical therapy versus surgical pericardiectomy.

3. Patients and Methods

3.1. Population

The medical records of the patients who were diagnosed with constrictive pericarditis in Rajaie Cardiovascular, Medical, and Research Center from October 2007 to December 2017 were reviewed. The diagnosis of constrictive pericarditis was confirmed by clinical presentation, transthoracic echocardiography, cardiac CT, Cardiovascular Magnetic Resonance (CMR) imaging, and cardiac catheterization, as appropriated. Patients with coronary artery disease were excluded from the study, because all-cause death, as the primary clinical endpoint of this study, might be affected by ischemic events in these patients. Patients with significant valvular heart disease and those who had undergone valve surgery were also excluded, because Doppler echocardiographic parameters, such as mitral inflow velocity, might be influenced by these clinical conditions, and mortality might result from valvular complications in such patients. Consequently, the medical records of 38 patients treated with conservative medical therapy were reviewed. Then, 38 patients who had undergone surgical pericardiectomy were randomly selected to be compared to the medical therapy group. The patients who had been diagnosed with post constrictive pericarditis within three months after cardiac surgery as well as those with acute pericarditis complicated with constrictive pericarditis were described as transient pericarditis.

The diagnosis of tuberculosis was confirmed on the basis of clinical findings in combination with histopathological features, including the presence of acid-fast bacilli in Ziel-Nelson tissue staining, typical granuloma and caseous necrosis, and bacteriological studies, using the Polymerase Chain Reaction (PCR) test on the pericardial fluid or tissue for the evidence of mycobacterium tuberculosis. Accordingly, six patients were diagnosed with tuberculosis, five had a history of chronic renal failure, and two had a history of previous cardiac surgery.

3.2. Treatment Method

The authors had no roles in the selection of the treatment methods, and type of treatment was selected by the physician based on the patients' conditions, risk of surgery, history of open heart surgery, and duration of the disease. Conservative medical therapy contained loop diuretics, salt restriction, anti-inflammatory agents (i.e., Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) or corticosteroids) for patients with inflammatory baseline disease (such as pericarditis), angiotensin-converting enzyme inhibitors, and anti-tuberculosis agents for the patients diagnosed with tuberculosis. It is worth mentioning that all the patients diagnosed with transient pericarditis were treated by conservative medical therapy.

3.3. Surgical Method

The primary surgical method was total pericardiectomy, including the resection of the anterior pericardium between the two phrenic nerves, the basal aspect of the pericardium over the diaphragm, the posterior part of the pericardium lying on the left and right ventricles, and the pericardium over the great arteries and both atria. Some patients could only undergo partial pericardiectomy because of inadequate exposure, high risk of coronary artery or myocardial damage, or severe bleeding. In such cases, the pericardium over the right atrium or superior and inferior vena cava was left intact. All procedures were done successfully without intra-hospital mortality or any serious post-operation complications.

3.4. Echocardiographic Examination and Doppler Filling Analysis

A comprehensive transthoracic Doppler echocardiographic study was performed using a Vivid 3 ultrasound imaging system (GE Healthcare, Milwaukee, WI) equipped with a 2.5-MHz transducer. All measurements were carried out

using the recommendations of the American Society of Echocardiography (15). Transmitral and transtricuspid flow velocity signals were obtained by placing a pulsed Doppler sample volume at the tips of the valve leaflets. Because all patients were in the sinus rhythm, three cycles were analyzed. For each transmitral and transtricuspid Doppler profile, the following variables were obtained: peak early (E) and late (A) transvalvular filling velocities. In addition, ejection fraction was calculated via the Simpson method. A constrictive pattern was defined as ≥ 25% increase in mitral E velocity with expiration compared to the inspiration phase as well as an augmented (≥ 25%) diastolic flow reversal in the hepatic vein after the onset of expiration compared to the inspiration phase.

3.5. Cardiac CT Scan and CMR Imaging

For all the patients whose clinical symptoms and echocardiography findings were suggestive of constrictive pericarditis, cardiac CT scan or CMR imaging was done for confirmation of the diagnosis. Pericardial thickness and brightness and maximum size of pericardial thickness were also obtained for each patient.

3.6. Statistical Analysis

Normally distributed continuous variables were reported as mean ± SD and were compared using student's t tests for unpaired observations. Intergroup comparisons were made using chi-square test. Besides, Wilcoxon's signed-rank test was used to compare the patients' New York Heart Association (NYHA) functional classes before and after the treatment. In all cases, $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 16.

The patients were followed up for at least 24 months and at most 144 months (median: 54 months) by periodical physical examinations and transthoracic echocardiography (6 months, 12 months, and then yearly after diagnosis). The 6- and 12-month follow-ups were successfully completed for all the 76 patients (100%). In addition, 58 patients (76.31%) were followed up for at least two years.

4. Results

The patients' baseline characteristics and echocardiographic features have been summarized in Table 1. In this study, one perioperative mortality (2.6%) occurred because of low-output and cardiogenic shock. The most common surgical pericardiectomy complication was severe bleeding (four patients, 10.5%) followed by sepsis (two patients, 5.2%) and hemodynamic instability (one patient, 2.6%). Inotropic agents were used for six patients (15.7%) during the first 24 hours and in two patients (5.2%) for more than 24 hours. All other patients (n = 37) were discharged successfully after surgery.

Pericardial thickness measured by cardiac CT scan or CMR imaging ranged from 1.6 to 17.4 mm (mean = 7.85 ± 3.17 mm) in the surgical pericardiectomy group and from 1.4 to 16.8 mm (mean = 6.93 ± 2.45 mm) in the conservative medical group, but the difference was not statistically significant (P = 0.16). The used medical treatments have been listed in Table 2.

Table 1. The Baseline Characteristics of the Patients

Variable			Number (%)		P-value
			Medical treatment (38 patients)	Surgery (38 patients)	
Mean age			51.68 ± 16.37	48.43 ± 17.04	0.36
Male			27 (71.0)	25 (65.7)	0.79
Female			11 (28.9)	13 (34.21)	0.42
Signs and symptoms	Dyspnea	FC I	3 (7.8)	2 (5.2)	0.64
	FC II		18 (47.3)	12 (31.5)	0.16
	FC III		14 (36.8)	20 (52.6)	0.16
	FC IV		3 (7.8)	4 (10.5)	0.68
	Edema		24 (63.1)	27 (71.0)	0.31
	Ascites		4 (10.5)	9 (23.6)	0.13
	Chest pain		10 (26.3)	14 (36.8)	0.34
	Syncope		0 (0)	1 (2.6)	0.86
Medical history	Cardiac surgery		2 (5.2)	0 (0)	0.15
	Radiation		0 (0)	1 (2.6)	0.86
	Malignancy		0 (0)	2 (5.2)	0.15
	Renal failure		1 (2.6)	4 (10.5)	0.18
	Tuberculosis		2 (5.2)	4 (10.5)	0.39
Echocardiography	LVEF (mean)		45.78±8.50	46.05 ± 7.54	0.88
	LVH		1 (2.6)	0 (0)	0.86
	Septal bounce		30 (78.9)	34 (89.4)	0.21
	IVC size (mean)		3.01 ± 5.17	2.78 ± 1.67	0.39
	IVC collapse (%)		29.4	24.6	0.31
	Pericardial effusion		16 (42.1)	13 (34.2)	0.48
Cardiac CT scan/ CMR	Pericardium	Normal	12 (31.5)	10 (26.3)	0.61
		Thickened*	17 (44.7)	18 (47.3)	0.82
		Thickened and calcified	7 (18.4)	12 (31.5)	0.18
		Pericardial thickness (mm)	6.93 ± 2.45	7.85 ± 3.17	0.16

Abbreviations: LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; IVC, inferior vena cava; CT scan, computed tomography scan; CMR, cardiovascular magnetic resonance imaging.

* Thickened pericardium defined as pericardium thickness > 3 mm in cardiac CT scan or CMR imaging.

The most common causes of the disease were idiopathic (64.4%) and tuberculosis (17.1%) followed by uremia (15.7%) and malignancy (6.5%). The final etiology of constrictive pericarditis in both groups has been shown in Table 3.

Among the 38 patients treated by conservative medical therapy, six were classified as transient constrictive pericarditis, two of whom had a recent open cardiac surgery (within three months) and four were diagnosed with acute pericarditis. In addition, 32 patients experienced at least one level decrease in NYHA functional class during the follow-up period (84.2%). On the other hand, dyspnea was decreased in 37 patients who had undergone surgical pericardiectomy (97.3%). This difference was not statistically significant (P = 0.05). The functional statuses of the two groups before and after the treatment have been depicted in Figures 1 and 2.

Edema was decreased in 15 out of the 24 patients who had been treated with conservative medical therapy (62.5%) and in 18 out of the 27 patients who had undergone surgical percardiectomy (66.6%), but the difference was not statistically significant (P = 0.74).

Among the four patients with ascites who had been treated with conservative medical therapy, only one had ascites during the follow-up. However, among the nine patients who had been treated with surgical pericardiectomy, none had ascites during the follow-up. Yet, the difference was not statistically significant (P = 0.13).

Based on the results, nine patients in the conservative medical therapy group had been re-hospitalized within the first year of treatment (23.8%), three of whom died during the follow-up period (33.3% of symptomatic patients and 7.8% of all patients). Among these patients, one had a history of open heart surgery, one had a history of tuberculosis, and one had a history of end-stage renal disease and heart failure. In the surgical pericardiectomy group, six patients had been re-hospitalized during the follow-up period (15.7%), two of whom died (33.3% of the re-hospitalized patients and 5.2% of all patients). One of these patients had a history of tuberculosis and the other one had a history of Hodgkin lymphoma and radiation. The decrease in the re-hospitalization rate after surgical pericardiectomy was not statistically significant compared to the conservative medical therapy group (P = 0.37).

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Table 2. The Medical Treatments Used in the Conservative Medical Therapy Group

Treatment	No (%)
Loop diuretics	38 (100)
NSAIDs	27 (71)
Corticosteroids	4 (10.5)
Anti-tuberculosis regimen	5 (13.1)
ACE inhibitor	15 (39.4)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs.

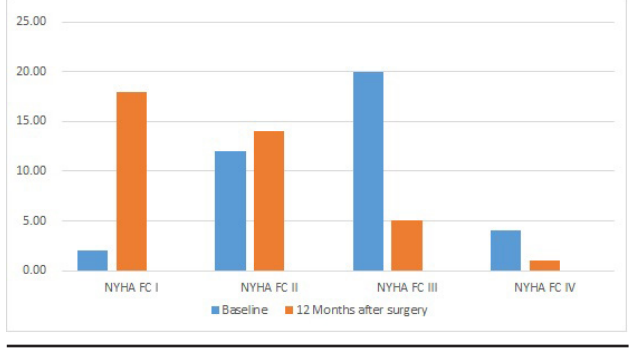

Figure 1. Comparison of New York Heart Association (NYHA) Functional Class before and after Surgical Pericardiectomy

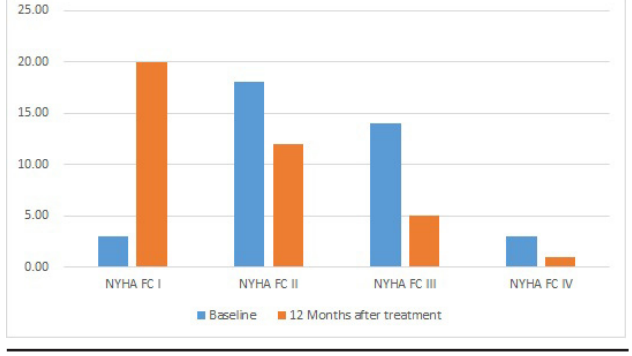

Figure 2. Comparison of New York Heart Association (NYHA) Functional Class before and after Conservative Medical Therapy

Table 3. The Etiologies of Constrictive Pericarditis

Etiology	Conservative Medical Therapy	Surgical Pericardiectomy
Idiopathic	27 (71.0%)	22 (57.8%)
Uremia	2 (5.2%)	4 (10.5%)
Malignancy	2 (2.6%)	3 (7.8%)
Radiation	0 (0)	1 (2.6%)
Tuberculosis	5 (13.1%)	8 (21.0%)
Prior cardiac surgery	2 (2.6%)	0 (0%)

patients and 5.2% of all patients). One of these patients had a history of tuberculosis and the other one had a history of Hodgkin lymphoma and radiation. The decrease in the re-hospitalization rate after surgical pericardiectomy was not statistically significant compared to the conservative medical therapy group (P = 0.37).

5. Discussion

Constrictive pericarditis has been defined as the chronic fibrous thickening of the wall of the pericardial sac, which leads to abnormal diastolic filling. The course of the disease is usually slow and the symptoms are nonspecific. Consequently, the symptoms may be present for 12 months or longer before a diagnosis is made in many cases. Congestive heart failure in the presence of normal left ventricular systolic functions should make us think about constrictive pericarditis. History, physical examination, electrocardiography, chest radiography, echocardiography, cardiac CT or MRI, and hemodynamic evaluation all are important modalities used for diagnosis (16).

Surgical pericardiectomy is an accepted type of treatment for the patients diagnosed with constrictive pericarditis. However, in some clinical scenarios such as transient constrictive pericarditis (i.e., post cardiac surgery), idiopathic constrictive pericarditis caused by inflammatory causes (i.e., pericarditis), and constrictive pericarditis after tuberculosis, medical treatment can be used and indiscriminate use of surgery can be avoided.

In the present study, the main causes of constrictive pericarditis were idiopathic and tuberculosis followed by uremia, malignancy, and radiation. In a study done by busch et al., the main causes were idiopathic, post-cardiac surgery, and post-mediastinal radiation followed by autoimmune diseases, tuberculosis, or rheumatic diseases (17). In another study by Biçer et al., the most common causes were tuberculosis, idiopathic, and malignancy (3).

In the current study, pericardial biopsy was not taken from the 38 patients treated by medical conservative therapy. Hence, definite diagnosis remained unclear in most of the cases. More investigations, such as pericardial biopsy, can obviously lead to the identification of more specific causes.

In the present research, the main symptoms were dyspnea and lower limb edema, which was in agreement with the findings of the previous studies (2, 17).

In this study, the most common NYHA function classes were II and III. In addition, dyspnea was reduced in both groups, with no significant differences between the two types of treatment. Prior studies have shown the effect of surgical pericardiectomy on reducing dyspnea in constrictive pericarditis (3, 18). The present study showed that medical therapy could also be useful in decreasing the level of dyspnea. Yet, these findings need to be approved in further studies with larger sample sizes. Moreover, the study results revealed a significant decrease in edema and ascites in both groups after the treatment. However, the difference between the two groups was not statistically significant. This finding could be attributed to the utilization of loop diuretics and salt restriction. Generally, conservative medical treatment by using loop diuretics, salt restriction, and NSAIDs, corticosteroids, or anti-tuberculosis regimens based on the cause of constrictive pericarditis can significantly decrease the symptoms of constrictive pericarditis, which can be comparable to surgical pericardiectomy. Nonetheless, future studies are recommended to approve these findings.

Surgical removal of the pericardium has been reported to be associated with a perioperative mortality rate of 5-10% in various large series. Besides, the operative mortality rate was strongly correlated to the preoperative NYHA class (6). In the current research, perioperative mortality rate was 2.6%, which was lower in comparison to the previous studies (6, 19). This could result from the smaller number of cases. Moreover, the mortality rate of the patients was similar in the two groups during the follow-up period. Thus, larger studies can be useful in this field.

Altogether, the present study findings revealed a significant reduction in the clinical symptoms and mortality rate of the patients diagnosed with constrictive pericarditis treated by conservative medical therapy.

5.1. Limitations

The limitations of the present study included its retrospective design, small number of patients, and relatively short follow-up period. Therefore, the findings might not be conclusive.

5.2. Conclusion

Conservative medical therapy based on the severity and cause of constrictive pericarditis could improve the clinical outcomes and symptoms, especially in patients with transient types of constrictive pericarditis as well as in those at a high risk for surgery. Surgical pericardiectomy also remains an effective treatment for constrictive pericarditis. Yet, these findings need to be confirmed in further studies with larger sample sizes.

5.2. Clinical Trial Registration Code

This was a retrospective study based on the review of medical records.

5.3. Ethical Approval

IR.IUMS.FMD.REC.1398.410 https://ethics.research.ac.ir/.

5.4. Informed Consent

Written informed consents were obtained from all the patients.

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Authors' Contribution

S.R., A.A., and M.M.P. conceived and designed the study and drafted the manuscript. M.E. and Z.R. participated in designing the study, performed some parts of the statistical analysis, and helped draft the manuscript. A.A. and M.M.P. reevaluated the clinical data, revised the manuscript, and performed the statistical analysis. E.G. and A.G. collected the clinical data, interpreted them, and revised the manuscript. N.A. and S.R. re-analyzed the clinical data and revised the manuscript. All authors read and approved the final manuscript.

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The authors have no financial interests related to the material in the manuscript.

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