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Efficacy and Safety of Nanocurcumin in Patients with Heart Failure Reduced Ejection Fraction; A Randomized Placebo-Controlled Clinical Trial

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ABSTRACT

Aims Heart failure reduced ejection fraction (HFrEF) is defined as symptoms, such as shortness of breath and edema with an ejection fraction of less than 40% in echocardiography. Regarding the pathogenesis, the role of inflammation is undeniable. Interleukin 6 (IL-6) is one of the pro-inflammatory cytokines that is important in cardiovascular disease and has a critical role in CAD. It is also related to complications caused by heart failure and mortality. Nanocurcumin is a polyphenol extracted from the rhizome of Curcuma longa (turmeric) with better bioavailability. Effects of nanocurcumin on the reduction of IL-6 and NT-proBNP in hospitalized HFrEF patients with acute decompensation were investigated.

Materials & Methods Sixty patients with HFrEF admitted with acute heart failure were divided into the intervention group with the administration of 40 mg of nanocurcumin twice a day for seven days and the control group (placebo). The levels of electrolytes, creatinine, IL-6, and NT-proBNP were measured at baseline and after one week.

Findings There was no statistically significant difference in the reduction in IL-6 and NT-proBNP levels in the intervention and control groups (p>0.05). Also, there was no significant difference in creatinine and estimated glomerular filtration rate in the two groups (p>0.05).

Conclusion Nanocurcumin at a dose of 40 mg twice a day for seven days in patients with acute decompensated heart failure did not reduce IL-6 and NT-proBNP levels.

Keywords Heart failure; Curcumin; Cardiovascular Diseases

CITATION LINKS

[1] Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ... [2] 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed ... [3] Sex differences in new-onset heart ... [4] Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: ... [5] Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic ... [6] A comprehensive population-based characterization of heart failure with ... [7] A contemporary appraisal of the heart failure epidemic in ... [8] Inflammation in heart failure: JACC state-of-the-art ... [9] The clinical significance of interleukin-6 in heart failure: ... [10] Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in ... [11] Curcumin in heart failure: A choice for complementary ... [12] Nanocurcumin: A promising candidate for therapeutic ... [13] Herbal medicine for cardiovascular diseases: Efficacy, mechanisms, ... [14] The prevalence of natural health product use in patients with acute ... [15] Novel nanomicelle formulation to enhance bioavailability and stability of ... [16] Inflammatory markers and incident heart failure in older men: The role of ... [17] The effects of curcumin on the prevention of atrial and ventricular arrhythmias and heart failure in patients with unstable angina: A randomized ... [18] The effect of nanocurcumin on the incidence of atrial fibrillation, and markers of inflammation and oxidative stress level after coronary artery bypass graft surgery: A randomized, double-blind, placebo-controlled ... [19] Three months of combination therapy with nano-curcumin reduces the inflammation and lipoprotein (a) in type 2 diabetic patients with mild to moderate coronary ... [20] Effects of curcumin on cardiovascular risk factors in obese and overweight adolescent girls: A randomized ... [21] Influence of enhanced bioavailable curcumin on obesity-associated cardiovascular disease risk factors and arterial function: A ... [22] The effect of 6 weeks of high intensity interval training (HIIT) with nano-curcumin supplementation on factors related to cardiovascular disease ... [23] Evaluation of Curcumin's effect on inflammation in hemodialysis ... [24] Inflammation–cause or consequence of heart failure or ...

Introduction

Heart failure (HF) is a clinical syndrome and includes the main cardiac symptoms (shortness of breath, fatigue, and edema) caused by structural or functional disorders. In HF, the internal pressure of the heart increases, which can lead to a decrease in the cardiac output. HF is often caused by myocardial dysfunction, which manifests as systolic or diastolic, or both [1]. Disturbance in the valves, pericardium, endocardium, or cardiac rhythm disorder can also be the cause of failure. In terms of classification based on ejection fraction (EF), we have three categories: HF with reduced EF (HFrEF): EF≤40%, HF with mildly reduced EF (HFmEF): 41%≤EF≤49%, and HF with preserved EF (HFpEF): EF≥50% [2]. In developed countries, such as Europe, the incidence of HF is 3 per 1000 person-years, and this ratio is 5 in 1000 in adults. The prevalence of HF in adults is 1-2%, which increases with age and reaches more than 10% in people over 70 years old. Usually, 50% of cases are HFrEF and 50% are HFpEF/HFmrEF [3, 4]. The causes of HF are diverse and differ based on geography. In developed and western countries, coronary artery disease and hypertension are the predominant causes [5] and HFrEF is more related to the etiology of coronary ischemia compared to HFpEF [6]. In general, despite the improvement of the prognosis in HF patients, the prognosis of these patients and their quality of life are still poor. The mortality rate in these patients is high, according to the Olmsted County cohort, the one-year mortality rate was 20% and the five-year mortality rate was 53% between 2000 and 2010 [7]. The mortality rate within five years from the time of diagnosis was 67% and among women, the mortality rate has been better than that of men. In general, survival in patients with HFpEF has been better than in HFrEF [7].

Acute heart failure (AHF) is a condition, in which HF symptoms appear quickly or gradually and require emergency cardiovascular care. This condition can be the first manifestation of HF and has a higher in-hospital mortality compared to the known cases of chronic HF.

In-hospital mortality in AHF is 4-10% and one-year mortality after discharge reaches 25-30%. The most common form of AHF is acute decompensated heart failure (ADHF), which is about 50-70% of AHF cases. This condition occurs mostly in patients with a history of HF, and unlike acute pulmonary edema, it usually develops gradually. Acute pulmonary edema is another manifestation of AHF, which is manifested by shortness of breath, orthopnea evidence of respiratory failure and tachypnea, and increased respiratory work [2].

One of the important processes in the pathophysiology of HF is inflammation. High levels of pro-inflammatory factors in HF patients are related to the deterioration of the clinical outcome and the process of ventricular remodeling. Interleukin 6 (IL-6) is one of the pro-inflammatory cytokines that is important in cardiovascular disease and has a critical role in CAD. It is also related to complications caused by HF, including AHF, anemia, worsening of hemodynamic conditions in advanced HF, as well as mortality caused by HF [8]. For this reason, the use of compounds that target IL-6 signaling pathways has become one of the interesting ideas in the treatment of HF. About half of patients with HF had IL-6 levels above the 95th percentile of the normal range. The increase in IL-6 levels will be an independent predictor of hospitalization due to HF and all-cause mortality. Also, as the level of estimated glomerular filtration rate (eGFR) decreases, the amount of IL-6 increases. Independent predictors of IL-6 include HFpEF, HF, iron deficiency, high levels of tumor necrosis factor/IL-1, Hepcidin, procalcitonin, and N-terminal fragment (NT)-pro-brain natriuretic peptide (ProBNP) [9].

Nanocurcumin is one of the anti-inflammatory and antioxidant compounds that can be effective in reducing the levels of inflammatory factors, especially IL-6 [10]. Curcumin is a polyphenol extracted from the turmeric and has various pharmacological activities. These activities include lipid-modifying, analgesic, and hypouricaemic, antioxidant effects. It also has anti-tumor, anti-thrombotic, anti-stress, and anti-depression effects and therapeutic effects in osteoarthritis and respiratory and cardiovascular diseases. Curcumin is effective in HF in vitro and in vivo, and these effects are due to improvement in ventricular hypertrophy and gene expression related to cardiomyocyte fibrosis [11]. The use of nanotechnology in the production of curcumin increases the biological benefits, drug delivery, and therapeutic effects [12].

Considering the high rate of using herbal medicines in today's medicine and the possibility of interference with the drugs used by patients with HF, it is necessary to investigate the effectiveness and safety of these compounds and educate patients on their correct and appropriate use [13, 14].

Materials and Methods

This is a randomized double-blind placebo-controlled clinical trial to evaluate the effect and safety of nanocurcumin in HFrEF patients conducted between October 2022 and January 2022. After approval of the ethics committee, this trial was registered at the Iranian Registry of Clinical Trials (IRCT20221007056110N1). The primary endpoint of this study was a reduction in IL-6 and NT-proBNP levels in patients with ADHF. The secondary endpoint was the effect of nanocurcumin on renal function.

Two homogeneous samples were selected as groups of case and control and the efficacy and safety of nanocurcumin were compared in the intervention and control groups (placebo). Using previous studies and the Pocock sampling method (comparison of the

standard deviation of two groups), the sample size was calculated. Confidence interval of 0.95 and type II error of 90% were considered, and other information was obtained from similar studies in each group, 30 patients were randomly included based on inclusion and exclusion criteria. The inclusion criteria were adults between 20 and 80 years old, a history of HFrEF due to ischemic and non-ischemic causes, ADHF, and signing the informed consent form. Exclusion criteria were active infection, acute kidney failure, rheumatological or underlying inflammatory diseases, symptoms of COVID-19, acute coronary syndrome (ACS) or stroke, hyperkalemia, dyspepsia, pregnancy, active bleeding, and the presence of symptoms of hypoperfusion or cardiogenic shock. Patients who had ACS or stroke, uncontrolled diseases, like hypertension, symptoms of gastrointestinal bleeding, hypotension, and cardiogenic shock, and those with missing doses for more than one day were excluded.

In the intervention group, a 40mg nanocurcumin capsule (SinaCurcumin, Iran) was given twice a day for seven days. In the control group, a placebo similar to the original drug made by the same company was used. The prescribed dose was based on the manufacturer's recommendation [15].

Laboratory tests, including NT-proBNP, IL-6, creatinine, GFR, electrolytes, and complete blood count were measured at baseline and after seven days. The results before and after the intervention were analyzed.

All patients in the nanocurcumin and placebo groups received standard treatments for ADHF according to the current global guidelines and no patient was deprived of the main treatments and guideline-directed medical therapy. IL-6 and NT-proBNP levels were measured by the ELISA method.

The results obtained from the laboratory tests were analyzed by SPSS version 20 and mean values were compared between the two groups using analysis of covariance, and the significant level was defined as less than 0.05.

Findings

In this study, 60 patients with HFrEF who were admitted with the diagnosis of ADHF were included based on the inclusion and exclusion criteria (Table 1).

Two groups were the same in age, gender, and cardiovascular risk factors, including diabetes, hypertension, history of myocardial infarction, family history of cardiovascular diseases, smoking, drug use, history of percutaneous coronary intervention (PCI), cardiac resynchronization therapy (CRT), coronary artery bypass grafting (CABG), and implantable cardioverter defibrillator (ICD) implantation, and there was no statistically significant difference between them (p-value>0.05). There was no significant difference in using HF therapeutic drugs, including neurohormonal inhibitors, beta-blockers, aldosterone inhibitors, SGLT2 inhibitors, and diuretics between the two groups (p-value>0.05). Initial tests at baseline included complete blood count, creatinine, electrolytes, NT-proBN, alanine aminotransferase (ALT), aspartate transaminase (AST), and IL-6 (Table 2). Complete blood count, creatinine, eGFR, AST, and ALT levels showed no statistically significant difference between the two groups (p-value>0.05).

Table 1. Frequency of demographic characteristics and risk factors of the subjects

	Intervention (n=30), %	Control (n=30), %	p-Value
Age (year), mean±SD	64.9±7.9	64.2±9.8	0.806
Male sex	75	65	0.490
Diabetes	40	30	0.507
Hypertension	45	55	0.527
Dyslipidemia	35	30	0.736
History of percutaneous coronary intervention	35	40	0.744
History of coronary artery bypass grafting	25	30	0.723
Implantable cardioverter defibrillator implantation	10	15	1.00
Smoking	35	50	0.337
Angiotensin receptor–neprilysin inhibitor	40	45	0.749
Angiotensin–converting enzyme inhibitors	30	35	0.736
Angiotensin receptor blockade	30	20	0.288
Using beta- blockers	90	80	0.661
Using SGLT2 inhibitors	50	45	0.752
Using alendronate inhibitors	65	70	0.736
Using diuretics	75	85	0.695
Sinus rhythm	70	70	1.00

Table 2. Basic tests of patients at baseline (mean±SD)

Tests	Intervention group (n=30)	Control group (n=30)	p-Value
White blood cell ($x10^9$/L)	6.87±2.38	6.81±1.94	0.925
Platelet ($x10^9$/L)	226.70±63.48	192.55±59.48	0.087
Hemoglobin (g/dl)	11.41±1.91	11.91±1.98	0.422
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	40.00±16.57	40.15±18.65	0.979
Creatinine (mg/dl)	2.24±1.38	2.17±1.3	1.00
Potassium (mmol/L)	4.35±0.69	4.67±0.58	0.122
alanine aminotransferase (U/L)	16.55±5.06	17.20±5.08	0.602
Aspartate transaminase (U/L)	27.55±7.81	26.90±5.23	0.759

In the intervention group, the mean levels of IL-6 before the intervention were 8.38pg/ml, which reached 6.44pg/ml after the intervention. In the control group, the mean levels of IL-6 before and after the intervention were 7.62 and 5.83pg/ml, respectively. There was no significant decrease in the levels of IL-6 in the intervention group compared to the control group (p-value=0.671) (Table 3).

Table 3. Results of laboratory tests before and after the intervention (mean±SD)

Tests	Intervention group	Control group	P-Value
Interleukin 6 (pg/ml) Baseline After 7 days	8.38±5.56 6.44±5.17	7.62 (5.83) 5.58 (4.47)	0.671
NT-proBNP (pg/ml) Baseline After 7 days	4596.95±1727.76 3487.25±1510.62	5055.1±1697.86 4058.65±1536.53	0.186
Creatinine (mg/dl) Baseline After 7 days	2.24±1.38 2.37±1.5	2.17±1.3 2.26±1.36	0.638
Estimated glomerular filtration rate (ml/min per 1.73m²) Baseline After 7 days	40±16.57 38.5±16.28	40.15±18.65 39.12±19.17	0.633

The mean levels of NT-proBNP in the intervention group were 4596.95pg/ml at baseline, which reached 3487.25pg/ml after the administration of nanocurcumin. In the control group, the mean levels of NT-proBNP before and after the intervention were 5055.1 and 4058.65pg/ml, respectively. The decrease in NT-proBNP levels in the drug group compared to the control group was not statistically significant (p-value=0.186).

The estimated marginal means of proBNP and IL-6 are shown in Figure 1.

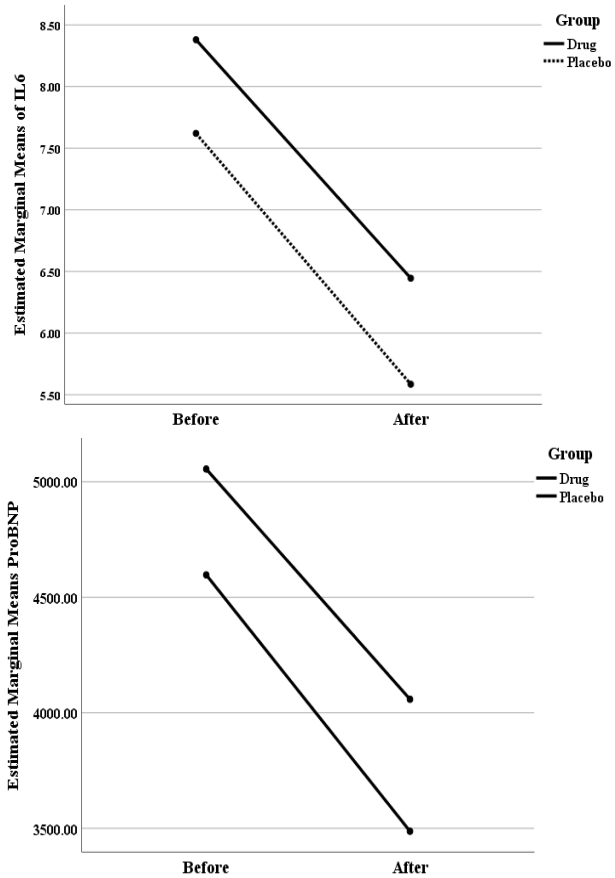

Figure 1. Estimated marginal means of proBNP and interleukin 6 (IL-6).

Discussion

HF is one of the big issues in the health system, which is associated with frequent hospitalizations. Treatment of chronic HF is a combination of diuretics, renin-angiotensin-aldosterone inhibitors, beta-blockers, aldosterone receptor inhibitors, SGLT2 inhibitors, and digoxin. The use of herbal compounds as complementary therapies has a long history in the treatment of diseases. Curcumin extracted from turmeric is known as one of the compounds with anti-inflammatory and antioxidant effects. Systemic inflammation is recognized as one of the known pathophysiologic features in both chronic and acute HF. It is also effective in predicting the development and progression of HF and the occurrence of possible complications, as well as clinical outcomes.

Increased levels of inflammatory biomarkers in the blood circulation, even in the absence of cardiovascular diseases, are associated with an increased risk of HF. IL-6 is one of the upstream inflammatory cytokines, which is involved in the initiation and extension of the atherosclerotic process [11]. Pro-inflammatory cytokines, such as IL-6 stimulate cardiac fibrosis and left ventricle remodeling. BNP and NT-proBNP are natriuretic peptides that are biomarkers of left ventricular failure and measurement of these markers is useful in diagnosing chronic or acute HF in symptomatic patients. Increased levels of these peptides are predictors of HF even in the absence of cardiovascular diseases [16]. In a cohort study, the increase in IL-6 levels was associated with iron deficiency, decreased left ventricular ejection fraction, atrial fibrillation, and poor clinical outcome [9].

In a study on the effect of nanocurcumin on the prevention of ventricular and atrial arrhythmias and HF in patients with unstable angina, administration of 80mg of nanocurcumin for five days had no effect on the occurrence of ventricular and atrial arrhythmias and echocardiographic indices, including diastolic function and pulmonary pressure [17].

In another study on the incidence of atrial fibrillation after coronary artery bypass grafting, the administration of 240mg of nanocurcumin could not reduce the incidence of atrial fibrillation after the procedure, and on the other hand, the levels of inflammatory markers, such as high sensitive C-reactive protein (hs-CRP), malondialdehyde, and glutathione were not significantly decreased [18]. Similarly, in our study, a daily dose of 80mg did not reduce the inflammatory marker IL-6.

In a clinical trial on the effect of nanocurcumin on cardiovascular inflammatory risk factors in diabetic patients with mild to moderate coronary artery disease, 80mg of nanocurcumin was given to 64 patients daily for 90 days in the nanocurcumin and placebo groups [19]. Lipid profile, lipoprotein, and hs-

CRP levels were measured at baseline and after 90 days. Nanocormin was able to significantly reduce the levels of hs-CRP and lipoprotein compared to the placebo. Nanocurcumin at 80mg daily reduced the progression of atherosclerosis by reducing the levels of hsCRP [19]. In our study, nanocurcumin could not reduce the levels of inflammatory cytokine IL-6 and also failed to reduce NT-proBNP levels. One of the possible reasons is the short period of intervention.

In a randomized placebo-controlled clinical trial conducted on 60 adolescent girls between 13 and 18 years old, the effect of 500mg curcumin daily on the risk factors of cardiovascular diseases was investigated compared to the placebo. After ten weeks, the significant effect of curcumin on body mass index, waist and thigh circumferences, high-density lipoprotein (HDL) levels, and triglyceride to HDL ratio was proven [20].

In a placebo-controlled clinical trial on 22 obese and young men aged 18-35 years, the effect of 500mg of curcumin daily for 12 weeks was evaluated. Blood samples and endothelial function were measured at baseline and after 12 weeks. The levels of homocysteine decreased in the curcumin group compared to the placebo group and the levels of HDL increased. In this study, there was no difference between the levels of glucose, insulin, leptin, adiponectin, and oxidative stress markers between the two groups. Also, there was no difference in endothelial function, augmentation index, and central blood pressure [21].

In another clinical trial on the effect of nanocurcumin compared to high-intensity interval training (HIIT) on the reduction of lipid profile and CRP levels, 48 overweight female students with a mean age of 21 years in the exercise, exercise+supplement, supplement, and control groups were assessed and received 80mg of nanocurcumin daily for six weeks. A significant decrease was observed in triglyceride and CRP levels in the exercise-supplement group compared to other groups [22].

Another study assessed the effect of curcumin on inflammatory factors in patients with end-stage renal disease. A total of 71 patients undergoing dialysis were divided into two treatment and control groups, and curcumin and placebo were prescribed for 12 weeks. Finally, curcumin was able to reduce the levels of TNF-alfa, IL-6, and hs-CRP, and increase the levels of albumin and there was no adverse drug effect [23].

In our study, patients with ADHF were treated with nanocurcumin and the levels of NT-proBNP and IL-6 were tested before and after the intervention. The dose given was 40mg two times a day for seven days. The patients in the two groups had no statistically significant differences in age and sex, risk factors, and drugs used. Treatment of ADHF was done according to the standard guidelines. The levels of NT-proBNP and IL-6 in the two groups did not have a statistically significant difference after the intervention, and this means that the administration of nanocurcumin at a dose of 40mg twice a day for one week has no effect on reducing the levels of NT-proBNP and IL-6. One of the reasons for using a low dose of nanocurcumin in our study was the fact that HF patients usually receive antiplatelet and anticoagulant regimens, and receiving a high dose of nanocurcumin can potentially increase the risk of bleeding. The short seven-day hospitalization period was also effective in shortening the treatment duration in these patients.

Inflammation can cause HF in many ways, such as intensification of atherosclerosis and endothelial dysfunction, the occurrence of acute coronary syndrome, and causing diabetes and obesity [24]. Despite the undeniable role of inflammatory mechanisms and inflammatory cytokines in the development and progression of cardiovascular diseases, especially HF, efforts to develop new anti-inflammatory drugs in the treatment of HF have been unsuccessful. One of the reasons is the lack of full understanding of the complex inflammatory network and its relationship with HF and the administration of anti-inflammatory drugs has not had enough effect in the clinical setting and in studies [8].

One of the strengths of this study is the selection of HF patients in an irreversible state and the use of herbal products with nanotechnology. However, the duration of treatment and a low dose of the prescribed product are the limitations. Due to the widespread use of herbal medicines in various diseases in our country, it is recommended to investigate the effect of these medicines on different diseases. In order to prevent indiscriminate use and to prevent drug interactions and possible complications, these patients, especially patients with HF who take a large number of drugs from different groups, should be given the necessary training.

Conclusion

Administration of 40 mg twice a day for seven days of nanocurcumin does not reduce the levels of NT-proBNP and IL-6 levels. Despite the strong association between inflammatory processes and ventricular remodeling and possible worsening of conditions, the administration of nanocurcumin at a dose of 40mg twice a day does not significantly reduce this process.

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Conflicts of Interests: None declared.

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