

Effect of intravenous nitrate treatment on serum BNP level and 30-day follow-up events in decompensated systolic heart failure

Dekompanze sistolik kalp yetmezlikli hastalarda intravenöz nitrat tedavisinin serum BNP seviyesi ve 30 günlük takip olayları üzerine etkisi

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ABSTRACT

Objective: The aim of this study was to evaluate the potential of intravenous (IV) nitroglycerine (NTG) administration to accelerate the reduction of B-type natriuretic peptide (BNP) levels in patients with decompensated systolic heart failure (HF) and to evaluate its impact on follow-up events.

Methods: A total of 165 patients with systolic HF who were hospitalized due to acute decompensation were enrolled into the current study. Study patients were divided into two groups. Patients who were receiving standard HF therapy (angiotensin-converting enzyme [ACE] or angiotensin receptor blocker [ARB], beta-blockers, loop diuretics, and anticoagulant or anti-aggregant agents for venous prophylaxis) were categorized as the standard HF therapy group (n=72), and patients receiving a standard dose of IV NTG in addition to standard HF therapy were categorized as the IV NTG group (n=93). BNP levels and blood gas analyses were measured at admission and after 48 h; all patients were followed up along the first month after discharge.

Results: Serum BNP levels decreased in all patients after 48 h. The decreasing of BNP level was higher and the improvement of blood gas analysis was better in the IV NTG group than in the standard therapy group (1347.1±314.3 vs. 280.0±196.2 pg/mL for the IV NTG group and 1178.3±305.5 vs. 495.4±229.9 pg/mL for the standard therapy group; p<0.001). In the multi-logistic regression analysis, serum sodium at admission, BNP level at 48 h, and use of IV NTG were found as predictors of 30-day follow-up events.

Conclusion: We have shown that IV NTG therapy in addition to standard HF therapy has a markedly better effect on lowering of plasma BNP levels, improves blood gas analyses, and may reduce follow-up events in patients with systolic HF.

Keywords: Intravenous nitrate, systolic heart failure, B-type natriuretic peptide

ÖZ

Amaç: Bu çalışmanın amacı intravenöz (IV) Nitrogliserin (NTG) tedavisinin akut dekompanze kalp yetmezlikli hastalarda B- tipi natriuretik peptid (BNP) seviyesinde azalma hızına ve takip olayları üzerine etkilerini incelemektir.

Yöntemler: Çalışmaya akut dekompanze kalp yetmezliği semptomları ile başvuran toplam 165 sistolik kalp yetmezlikli hasta alındı. Hastalar 2 gruba ayrıldı. Standart tedavi (ACE veya ARB, beta-bloker, loop diuretiği ve venöz profilaksi için antikoagülan veya anti-agregan ajan) alan grup (72 hasta) ve standart tedaviye ek olarak intravenöz Nitrogliserin alan hastalar (93 hasta) IV NTG grubu olarak ayrıldı. Tüm hastalardan başvuruda ve 48 saat sonra BNP ve arteriyel kan gazı örnekleri alındı ve hastalar ilk 1 ay boyunca takip edildi.

Bulgular: Serum BNP seviyeleri tüm hastalarda 48 saat sonra azaldı. IV NTG grubunda serum BNP seviyelerinde azalma ve kan gazı değerlerinde iyileşme standart tedavi grubuna göre daha iyi bulundu (NTG grubu değişimi: 1347,1±314,3 vs 280,0±196,2 pg/mL Standart grup değişimi: 1178,3±305,5 vs: 495,4±229,9 pg/mL; p<0,001). Multi-lojistik analizde başvurudaki sodyum değeri, 48. saatteki serum BNP değeri ve IV NTG kullanımı 30 günlük olaylar için prediktif olarak bulundu.

Sonuç: Plazma BNP değerlerini belirgin olarak azaltan ve kan gazı değerlerinde düzelme sağlayan intravenöz nitrogliserin tedavisinin standart tedaviye eklenmesi sistolik kalp yetmezlikli hastalarda takip olaylarını azaltabilir.

Anahtar kelimeler: İntravenöz nitrat, sistolik kalp yetmezlik, B- tipi natriuretik peptid

INTRODUCTION

Systolic heart failure (HF) is one of the most common reasons for re-hospitalization and associated with substantially increased morbidity and mortality (1-3). In clinical practice, vasodilators and diuretics are the primarily used therapies for relieving symptoms in patients with systolic HF during decompensation (4). Although nitrates have been used for over a century for the treatment of angina pectoris as a coronary vasodilator agent, it has also been used to provide vasodilation in patients with systolic HF.

A number of studies have suggested that organic nitrates could result in clinical improvement, and there is a strong, rational, physiologic reason for their use in HF patients (5). Recently, Breidhardt investigated the safety and efficacy of sublingual and transdermal nitrates in patients with acute HF and found that patients treated with noninvasive nitrates in addition to standard HF therapy had better outcomes. The authors concluded that the beneficial effect of nitrate on patients' outcome was primarily due to the reduced effect of nitrates on B-type natriuretic peptide (BNP) levels. In fact, as a strongly independent predictor of mortality in both acute and chronic systolic HF, BNP has been evaluated in several HF studies, and its level was shown to diminish with nitrate therapy due to a fall in afterload and preload (6-8). BNP can also predict clinical outcomes in patients with systolic HF as well as at admission and discharge periods (9).

In contrast, recent research suggest that nitrates are used sporadically in clinical practice and appear to be less standardized in decompensated HF due to the lack of high-quality evidence that supports the use of these agents, especially the intravenous (IV) forms (10-13). Hitherto, no data are available on the effect of the IV form of nitroglycerine (NTG) on HF with reduced ejection fraction (HFREF) outcomes, such as death and re-hospitalization during acute decompensation and after discharge. In this study, we aimed to investigate the effect of IV NTG on serum BNP levels and evaluate its effect on follow-up events in patients with acute decompensated systolic HF to demonstrate a clinical benefit of IV NTG in terms of mortality and major morbidity.

METHODS

A total of 165 consecutive patients with systolic HF who were hospitalized because of acute decompensation were prospectively enrolled into the current study. HF was defined as current symptoms of disease, or a history of symptoms controlled by ongoing therapy, in the presence of reduced left ventricular (LV) systolic function ($\leq 45\%$) on transthoracic echocardiography, and in the absence of any other cause for symptoms (14, 15). Patients were divided into two groups. The IV NTG group included 93 patients receiving standard IV NTG (a standard nitrate infusion of between 0.3 and 0.5 $\mu\text{g}/\text{kg}/\text{min}$) in addition to the standard HF therapy (angiotensin-converting enzyme [ACE] or angiotensin receptor blocker [ARB], beta-blockers, mineralocorticoid receptor antagonists, loop diuretics, and anticoagulant agents for deep venous prophylaxis); the standard therapy (ST) group included 72 patients treated with only the standard HF therapy.

Patients with hypotension (systolic blood pressure < 100 mmHg) or in cardiogenic shock with acute coronary syndrome, severe

aortic stenosis, presence of any acute or chronic inflammatory disease, any known malignancy, acute, or chronic hepatic failure, chronic kidney disease that required hemodialysis, and previous adverse reactions to nitrate therapy were excluded from the study. All participants' age, sex, and duration of HF were recorded. Informed consent was obtained from all study patients, and the study protocol was approved by the local ethics committee.

Laboratory Tests

Serum samples for hematologic and biochemical parameters, including BNP, were collected from a peripheral vein in the intensive care unit (ICU) and measured using an automated chemistry analyzer with commercial kits (Beckmann Assay 360, Bera, California, USA). The BNP levels were assessed using immunoturbidimetry at admission, after 48 h, and at a 1-month follow-up examination. Hematologic parameters were measured from tripotassium ethylenediaminetetraacetic acid-based anti-coagulated blood samples and assessed using a Sysmex K-1000 auto-analyzer within 30 min of sampling. Samples for blood gas analyses were collected via radial artery puncture at admission and at 48 h.

The study patients were followed up throughout the first month. Follow-up events were defined as death and/or re-hospitalization for cardiac dyspnea or rapid congestion as a sign of decompensation. In addition, patients were questioned if they had been re-hospitalized at any other clinic during the follow-up period.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) software (SPSS version 16.0, Chicago, IL, USA) was used for the statistical analysis. Descriptive statistical methods, such as mean, standard deviation, interquartile range, frequency distributions, and independent t-test for comparison of groups of binary variables with normal distribution were used. The Mann-Whitney U test was used for the comparison of two groups with abnormal distribution of variables, and the Chi-square test was used for comparison of qualitative data. Logistic regression analysis was used to identify factors that may predict 30-day follow-up events. A p value < 0.05 was accepted to be statistically significant.

RESULTS

The baseline characteristics of the study patients are summarized in Table 1. Baseline demographic, laboratory, and echocardiographic parameters of the groups were similar. The outpatient medication and medications given in the ICU setting including the amount of diuretics were also similar in both groups. In laboratory analyses, blood gas analysis parameters and mean BNP level were similar between the two groups ($p=0.41$ for BNP, $p=0.38$ for SpO_2 , $p=0.21$ for SpCO_2 , $p=0.73$ for HCO_3 , and $p=0.33$ for O_2 saturation.); none of the study patients had metabolic or respiratory acidosis at admission (Table 1).

Table 2 displays the characteristics of groups after 48 h of treatment. Although BNP levels were decreased in both groups, the amount of decrease in BNP level was higher in the NTG group than that in the ST group (80% of initial level in IV NTG group and 50% of initial level in the ST group, $p<0.001$). The follow-up pO_2

Table 1. Baseline characteristics of the study groups

| | IV NTG group (n=93) | ST group (n=72) | p |
|---|---------------------|-----------------|------|
| Age, years, mean±SD | 67.3±8.5 | 66.4±8.4 | 0.76 |
| Sex, n (%), female | 35 | 65 | 0.40 |
| Medical history, (%) | | | |
| Hypertension | 49 | 51 | 0.28 |
| Diabetes mellitus | 60 | 40 | 0.13 |
| Chronic kidney disease | 48 | 52 | 0.26 |
| Outpatient medication use, (%) | | | |
| Beta-blockers | 48 | 47 | 0.36 |
| ACE Inhibitors/AT-Antagonists | 50 | 52 | 0.29 |
| MRA | 53 | 55 | 0.36 |
| Nitrates | 47 | 49 | 0.36 |
| Loop diuretics | 74 | 69 | 0.22 |
| Given HF therapies in the ICU | | | |
| Beta-blocker, number of treated patients (%) | 46 | 51 | 0.64 |
| ACE inhibitors, number of treated patients, (%) | 61 | 77 | 0.44 |
| MRA, number of treated patients, (%) | 47 | 57 | 0.52 |
| Loop diuretics, number of treated patients, (%) | 78 | 81 | 0.62 |
| Anticoagulants, number of treated patients, (%) | 88 | 94 | 0.38 |
| Vital signs, mean±SD | | | |
| Systolic blood pressure, mmHg | 138.5±22.3 | 130.4±15.9 | 0.13 |
| Diastolic blood pressure, mmHg | 81.4±10.8 | 80.0±10.2 | 0.63 |
| Heart rate, bpm | 99.1±24.1 | 87.0±20.3 | 0.06 |
| Laboratory parameters, mean±SD | | | |
| Hemoglobin, g/dL | 11.2±1.7 | 11.8±2.8 | 0.25 |
| Serum creatinine, mg/dL | 1.7±0.9 | 1.6±0.8 | 0.42 |
| Serum urea, mg/dL | 33.2±7.5 | 31.8±8.4 | 0.62 |
| Serum sodium, mg/dL | 134.2±9.4 | 136.2±9.7 | 0.48 |
| BNP, pg/mL | 1347.1±314.3 | 1178.3±305.5 | 0.41 |
| Hs-CRP, mg/L | 1.6±1.4 | 2.0±2.1 | 0.33 |
| Blood gas analyses | | | |
| SpO ₂ , mmHg | 63.1±14.7 | 67.9±26.1 | 0.38 |
| SpCO ₂ , mmHg | 43.0±14.7 | 38.3±14.1 | 0.21 |
| HCO ₃ , mmol/L | 21.8±4.6 | 21.4±4.7 | 0.73 |
| pO ₂ saturation, % | 89.0±3.4 | 90.0±4.1 | 0.33 |
| Echocardiographic findings, mean±SD | | | |
| LVEF, % | 33.6±11.1 | 33.2±9.9 | 0.88 |
| LVsD, cm | 4.5±0.8 | 4.6±0.9 | 0.96 |
| LVdD, cm | 5.8±0.8 | 5.7±1.0 | 0.39 |
| IVsD, cm | 1.24±0.2 | 1.21±0.2 | 0.71 |
| PwD, cm | 1.18±0.2 | 1.19±0.2 | 0.95 |

MRA: Mineralocorticoid receptor antagonist; BNP: B-type natriuretic peptide; Hs-CRP: High sensitive C-reactive protein; ST: Standard therapy; SpO₂: Peripheral oxygen saturation; SpCO₂: Peripheral carbon dioxide saturation; HCO₃: Bicarbonate; LVEF: Left ventricular Ejection fraction; LVsD: Left ventricular systolic diameter; LVdD: Left ventricular diastolic diameter; IVsD: Interventricular septum diameter; PwD: Posterior wall diameter; SD: standard deviation; IV: intravenous; ACE: Angiotensin-converting enzyme; ICU: Intensive care unit; NTG: Nitroglycerine; p<0.05 was accepted as significant

Table 2. Comparison of the clinical characteristics of patients per groups after 48 h

| | NTG group (n=93) | ST group (n=72) | p |
|--------------------------------|---------------------|--------------------|--------|
| Diuretic, total dose, mg | 42.5±7.5 | 44.5±8.5 | 0.56 |
| Vital signs, mean±SD | | | |
| Systolic blood pressure, mmHg | 121.5±21.9 | 129.5±32.1 | 0.23 |
| Diastolic blood pressure, mmHg | 80.5±12.0 | 82.1±8.3 | 0.51 |
| Laboratory parameters | | | |
| Serum creatinine, mg/dL | 1.8±0.97 | 1.61±0.84 | 0.53 |
| Serum urea, mg/dL | 37.2±8.4 | 34.3±8.1 | 0.37 |
| BNP, pg/mL | 280.0±196.2 | 495.4±229.9 | <0.001 |
| Blood gas analyses | | | |
| SpO ₂ , mmHg | 83.3±9.5 | 74.5±8.4 | <0.001 |
| SpCO ₂ , mmHg | 34.4±6.4 | 40.5±13.3 | 0.028 |
| HCO ₃ , mmol/L | 25.1±4.6 | 24.3±4.5 | 0.72 |
| O ₂ saturation, % | 92.9±2.8 | 93.4±3.3 | 0.43 |
| Diuretic, total dose, mg | 42.5±7.5 | 44.5±8.5 | 0.38 |

BNP: Brain natriuretic peptide; HCO₃: Bicarbonate; SpO₂: Peripheral oxygen saturation; SpCO₂: Peripheral carbon dioxide saturation; ST: Standard therapy; NTG: Nitroglycerine; SD: Standard deviation; p<0.05 was accepted as significant

Table 3. Comparison of the two groups at the end of the follow-up period

| | NTG group (n=93) | ST group (n=72) | p |
|-----------------------|---------------------|--------------------|--------|
| Number of events, n | 16 | 27 | 0.003 |
| Death, n | 5 | 9 | 0.1 |
| Re-hospitalization, n | 11 | 18 | 0.027 |
| BNP value, pg/mL | 332±228 | 654±226 | <0.001 |

BNP: Brain natriuretic peptide; ST: Standard therapy; NTG: Nitroglycerine; p<0.05 was accepted as significant

and pCO₂ saturations were improved after 48 h in both groups; the follow-up pO₂ saturation was higher and follow-up pCO₂ saturation was lower than the initial levels in both groups. However, the follow-up pO₂ and pCO₂ saturations were more improved compared with baseline in the IV NTG group than those in the ST group (Table 2).

Follow-up events were defined as death and/or re-hospitalization. In the 30-day follow-period, the total number of events seen among patients in IV NTG group was 16 (5 deaths and 11 re-hospitalizations) and 27 patients (9 deaths and 18 re-hospitalizations) in the ST group (p=0.027 for re-hospitalization, p=0.1 for death, and p=0.003 for total events). The BNP values were also higher in the ST group than those in the IV NTG group at the end of follow-up (654±226 vs. 332±228 pg/mL, p<0.001; Table 3).

Table 4. Multi-logistic regression analysis results for predicting follow-up month events

| | Odds ratio (95% CI) | p |
|-------------------------|---------------------|--------|
| Age, | 1.0 (0.96-1.50) | 0.82 |
| Sex, female | 1.6 (0.48-5.7) | 0.43 |
| Serum creatinine | 1.1 (0.67-1.75) | 0.72 |
| Hemoglobin | 1.12 (0.56-1.65) | 0.61 |
| Hs-CRP | 1.13 (0.86-1.47) | 0.36 |
| Serum sodium | 0.92 (0.88-0.96) | 0.001 |
| Using IV NTG | 7.7 (2.26-26.6) | 0.001 |
| BNP levels on admission | 1.01 (0.85-1.2) | 0.34 |
| BNP levels at 48 h | 0.99 (0.98-1.0) | <0.001 |
| Heart rate | 0.95 (0.88-1.01) | 0.20 |
| Systolic blood pressure | 1.02 (0.98-1.04) | 0.21 |

BNP: Brain natriuretic peptide; Hs-CRP: High sensitive C-reactive protein; CI: Confidence interval; IV NTG: Intravenous nitroglycerine; p<0.05 was accepted as significant

In the multi-logistic regression analyses, sodium level at admission, BNP at 48 h, and use of IV NTG were found as predictors of 30-day follow-up events (Table 4).

DISCUSSION

The main finding of this study was that IV NTG, which has favorable effects on cardiovascular hemodynamics, may also have an effect on the outcomes of patients with systolic HF. This is the first study to report that IV NTG may improve HF patients' outcomes during hospitalization and reduce firstmonth adverse events following discharge.

All available forms of organic nitrates have been widely used in cardiovascular medicine. In clinical practice, IV nitrate infusion has been used to reduce pulmonary capillary wedge pressure and systemic vascular resistance in patients with HF who have pulmonary congestion/edema with systolic blood pressure >110 mmHg. Organic nitrates mainly produce dilatation in veins, arteries, and arterioles. All the forms (oral, IV, or transdermal) have an effect that substantially reduces right and LV filling pressure, systemic vascular resistance, and systemic blood pressure due to the decreased LV filling pressure and improves forward cardiac output and stroke volume (16). All these hemodynamic effects of organic nitrates can provide symptomatic relief in systolic HF during acute decompensation.

The current data about nitrate use in decompensated HF patients are based on a review that included a few low-quality studies, and studies regarding its effect on mortality are limited (5). Moreover, the beneficial effect of IV form of NTG on the outcomes of HF patients has not been previously studied. In the current study, we showed an early benefit of IV nitrate in terms of re-hospitalization and death throughout the first month following discharge. In this regard, the current study results are important. In

the V-HeFT trial, the combination of hydralazine and isosorbide dinitrate (ISDN) decreased the 2-year mortality of patients with HF compared with placebo (17). After the encouraging results of the V-HeFT study on mortality, organic nitrates have been extensively studied regarding the outcomes in patients with HF in clinical practice. In one such study by Cotter et al. (18), 110 patients with HF were randomized to receive a high-dose nitrate in addition to a low-dose diuretic and a high-dose diuretic with a low-dose ISDN infusion. The authors found a significant reduction in the need for ventilation and incidence of myocardial infarction (MI), as well as a trend toward less mortality in the high-dose nitrate/low-dose diuretic group. In another nitrate trial, 40 patients were randomized to receive 4 mg ISDN every 4 min or bi-level positive airway pressure (BiPAP) plus a standard-dose ISDN infusion starting at 10 $\mu\text{mol}/\text{min}$ and increased every 5–10 min, which is considered a conventional treatment. The researchers found a lower mortality rate (0% compared with 40%) in the 4 mg ISDN group, less need for mechanical ventilation (20% compared with 80%), and a lower incidence of MI (10% compared with 55%) (19). Recently, Breidhardt showed that sublingual and transdermal nitrates had an improving effect on the mortality in patients with acute HF. Breidhardt showed that high-dose sublingual or transdermal nitrate on top of standard HF therapy was safe and accelerated cardiac recovery (20). In another study, it was found that IV nitrate improved cardiac function in patients with acute HF due to severe aortic stenosis (21), in which vasodilators are generally thought to be contraindicated.

In our study, there was no hospital mortality among the study patients. Furthermore, IV NTG on top of ST was well tolerated and laboratory parameters of patients were not affected by nitrate therapy in the IV NTG group. We followed up all patients through the first month after discharge. The therapies throughout follow-up were similar between the groups. Although BNP levels were elevated in both groups at the end of first month, patients who were treated with IV nitrate therapy during hospitalization had lower BNP levels. Also, the rate of re-hospitalization was lower in the IV NTG group than that in the ST group during the follow-up period. The use of IV NTG was found a predictor of the following adverse events according to our logistic regression analyses results. The beneficial effect of IV NTG on first month events may be explained by two possible mechanisms. First, patients in the IV NTG group had lower level of BNP during discharge and at the end of follow-up period. We evaluated cardiac recovery through measurements of BNP levels. We found that if the IV NTG therapy was initiated early after patient admission, it could accelerate cardiac recovery, as assessed by serum BNP, which was found lower in the IV nitrate group compared with the ST alone within the first 48 h of treatment. As a natriuretic peptide, BNP is released from cardiomyocytes in response to pressure or volume-overloaded states, and its plasma levels are an independent predictor of outcomes in HF and elevated levels are associated with poor prognosis (22). We adjusted all factors that might contribute toward the decrease of BNP levels. Due to the effect on serum BNP level, we attempted to homogenize the groups in terms of given medication, such as diuretics, ACE inhibitors, and beta blocking agent. Also, the groups were similar in terms of previous medications, initial BNP levels, and echocar-

diographic and hemodynamic findings. After adjusting all these factors, we found that the decrease in BNP was higher in the IV NTG group than that in the ST group at the end of 48 h. The BNP values reduced more and faster in the IV NTG group, probably due to the reduction in ventricular filling pressures and the increase in cardiac output due to the NTG therapy. The dilatation in veins leads to a reduction of venous return to the right ventricle. Thus, the LV preload is decreased. This is potentially beneficial in systolic HF. We thought that the lower re-hospitalization rate in the IV nitrate group may also be explained by the effect of IV NTG on blood gas analysis results as well as its lowering effect of serum BNP level. Thus, the beneficial effects of IV nitrates on blood gas analysis were previously described in two randomized trials. It was shown that nitrates can decrease the need for mechanical ventilation as well as lower the incidence of MI in patients with pulmonary edema (18). Moreover, high-dose IV nitrates improved outcomes in patients with pulmonary edema compared with standard doses of nitrates (19). In this regard, our findings about blood gas analysis were in line with previous studies. Finally, the lower discharge BNP level may explain why the patients treated with IV NTG had lower re-hospitalization rate throughout first month. It was previously shown that BNP levels >400 pg/mL at 30 days after discharge or with an increase of $>4\%$ at follow-up could predict repeated re-hospitalization and death (23).

Limitations

Although the sample size is similar to previous larger studies, the most important limitation of our study is the short follow-up period. Also, the evaluation of renal function and respiratory parameters over a longer observational period should be performed. In contrast, the randomization was well matched based on the patients' baseline characteristics, disease severity, and treatments. All of these randomizations were similar to those observed in large registry studies.

CONCLUSION

This is the first study to evaluate the clinical benefit of IV NTG in acute decompensated phase of systolic HF. The IV NTG therapy in addition to standard HF therapy can accelerate cardiac recovery as quantified by BNP level, improve blood gas analyses within the first 48 h of treatment in the ICU, and may reduce adverse events during the first month following discharge.

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

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

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