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The Efficacy of Nitrite Therapy for the Treatment of Heart Failure: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: The efficacy of nitrite therapy for the treatment of heart failure remains controversial. We conducted a systematic review and meta-analysis to explore the impact of nitrite therapy on heart failure.

Methods: We searched the PubMed, EMbase, Web of Science, EBSCO, and Cochrane Library databases through November 2019 for randomized controlled trials (RCTs) assessing the effect of nitrite therapy on heart failure. This meta-analysis was performed using the random-effect model.

Results: Three RCTs are included in the meta-analysis. Overall, compared with the control group for heart failure, nitrite therapy is associated with significantly reduced PCWP (Std. MD=-1.22; 95% CI=-1.81 to -0.63; $P < 0.0001$) and improved PAC (Std. MD=0.71; 95% CI=0.16 to 1.27; $P = 0.01$), but reveals no substantial influence on peak VO2 (Std. MD=-0.19; 95% CI=-0.49 to 0.11; $P = 0.21$), systolic BP (Std. MD=-3.98; 95% CI=-8.24 to 0.28; $P = 0.07$), mean BP (Std. MD=-1.53; 95% CI=-3.37 to 0.31; $P = 0.10$), or heart rate (Std. MD=0.40; 95% CI=-0.14 to 0.94; $P = 0.15$).

Conclusions: Nitrite therapy may show some benefits to heart failure.

INTRODUCTION

Heart failure widely occurs in clinical work, and the etiology of heart failure mainly includes ischemic and non-ischemic causes [Francis 2019; McMurray 2019; Solomon 2019]. Ischemic or non-ischemic cardiomyopathy classification has important prognostic implications [Felker 2002; Lipinski 2017]. Only 50% patients with heart failure have a preserved ejection fraction. Accumulating evidence suggest that impairments in nitric oxide availability plays important roles in the pathophysiology of heart failure [Paulus 2013; Shah 2008]. Therapies targeting the nitric oxide pathway have been explored to treat heart failure, but a clear benefit is not observed [Redfield 2013; Redfield 2015; Pieske 2017].

The inorganic nitrate/nitrite pathway represents a different means of restoring nitric oxide signaling [Reddy 2017]. Unlike the organic nitrates such as isosorbide mononitrate and dinitrate, inorganic nitrite is converted to nitric oxide in a 1-step reaction in the presence of hypoxia and acidosis, which can be facilitated by exercise. Several acute and short-term, single-center studies have documented improved cardiac hemodynamics and exercise capacity with inorganic nitrate/nitrite in patients with heart failure [Borlaug 2015; Zamani 2015; Eggebeen 2016; Simon 2016; Zamani 2017].

The efficacy of nitrite therapy for heart failure has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [Borlaug 2015; Borlaug 2018; Borlaug 2016]. With accumulating evidence, we therefore performed a systematic review and meta-analysis of RCTs to investigate the efficacy of nitrite therapy in patients with heart failure.

MATERIALS AND METHODS

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis were conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [Moher 2009].

Search strategy and study selection: Two investigators independently searched the following databases (inception to December 2019): PubMed, EMbase, Web of Science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: nitrite, and heart failure. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients with heart failure; (ii) intervention: nitrite therapy; (iii) comparison: placebo; (iv) study design: RCT.

Data extraction and outcome measures: We extracted the following information: author, number of patients, age, female, body mass index, NT-proBNP and detail methods in each group, etc. Data independently was extracted by two

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investigators, and discrepancies were resolved by consensus. We also contacted the corresponding author to obtain data, when necessary.

The primary outcomes are pulmonary capillary wedge pressure (PCWP) and pulmonary artery compliance (PAC). Secondary outcomes include peak oxygen consumption (VO2), systolic blood pressure (BP), mean BP, and heart rate.

Quality assessment in individual studies: Methodological quality of the included studies is independently evaluated using the modified Jadad scale [Jadad 1996]. There are three items for Jadad scale: randomization (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-1 points). The score of Jadad scale varies from 0 to 5 points. An article with Jadad score≤2 is considered to be of low quality. If the Jadad score≥3, the study is thought to be of high quality [Kjaergard 2001].

Statistical analysis: We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (PCWP, PAC, peak VO2, systolic BP, mean BP, heart rate). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I2 statistic, and I2 > 50% indicates significant heterogeneity [Higgins 2002]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

RESULTS

Literature search, study characteristics and quality assessment: A detailed flowchart of the search and selection results was shown in Figure 1. (Figure 1) After the initial search of databases, 275 publications were searched. Eighty-six duplicates and 184 papers after checking the titles/abstracts were excluded. Two studies were removed because of the study design and three RCTs ultimately were included in the meta-analysis [Borlaug 2015; Borlaug 2018; Borlaug 2016].

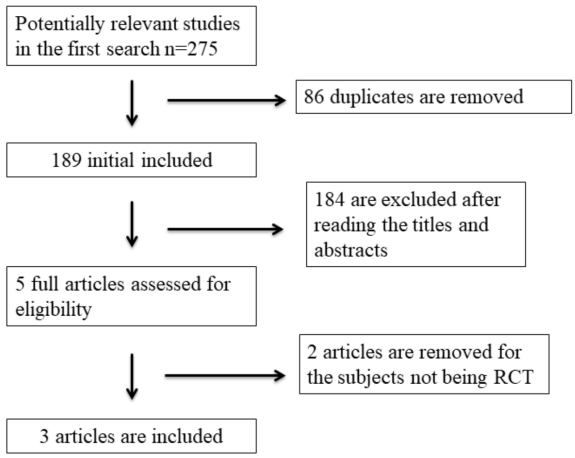

Figure 1. Flow diagram of study searching and selection process

Table 1. Characteristics of included studies

NO. Author	Nitrite group						Control group						Jada scores
	Number	Age (years)	Female (n)	Body mass index (kg/m2)	NT-proB-NP (pg/mL)	Methods	Number	Age (years)	Female (n)	Body mass index (kg/m2)	NT-proB-NP (pg/mL)	Methods	
1 Borlaug 2018	53	68 (9)	36	35.6 (6.4)	471 (624)	Inhaled nitrite at 46 mg 3 times a day for 1 week followed by 80 mg 3 times a day for 3 weeks	52	68 (12)	23	35.0 (7.0)	528 (669)	Matched placebo	5
2 Borlaug 2016	13	67 (9)	6	33.2 (30.3, 38.2)	551 (66, 1227)	Inhaled sodium nitrite (90 mg)	13	72 (10)	8	30.8 (24.3, 36.0)	977 (196, 3683)	Matched placebo	4
3 Borlaug 2015	14	69 (6)	9	32.0 (7.0)	249 (118-890)	Infusion of sodium nitrite (50 mg/kg/min)	14	70 (8)	8	33.4 (6.6)	585 (107-1575)	Matched placebo	3

Values are mean (SD) or median (interquartile range)

The baseline characteristics of three eligible RCTs in the meta-analysis are summarized in Table 1. (Table 1) The three studies were published between 2015 and 2018, and sample sizes ranged from 28 to 105, with a total of 159. Two included RCTs reported inhaled nitrite [Borlaug 2018; Borlaug 2016], while the remaining RCT reported infusion of sodium nitrite [Borlaug 2015].

Among the three studies included here, two studies reported PCWP and PAC [Borlaug 2015; Borlaug 2016], three studies reported peak VO2, systolic BP and mean BP [Borlaug 2015; Borlaug 2018; Borlaug 2016], and two studies reported heart rate [Borlaug 2015; Borlaug 2016]. Jadad scores of the three included studies varied from 3 to 5, and all three studies were considered to be high-quality ones, according to quality assessment.

Primary outcomes – PCWP and PAC: PCWP were measured at end-expiration (mean of ≥3 beats) using 2-F, high-fidelity micromanometer-tipped catheters advanced through the lumen of a 7-F, fluid-filled catheter. PAC represented the stroke volume/pulmonary artery pulse pressure. These two outcomes were important to measure the cardiac function and analyzed with the random-effects model.

Compared with the control group for heart failure, nitrite therapy resulted in significantly reduced PCWP (Std. MD=-1.22; 95% CI=-1.81 to -0.63; $P < 0.0001$) with no heterogeneity among the studies (I2=0%, heterogeneity $P = 0.79$) (Figure 2) and increased PAC (Std. MD=0.71; 95% CI=0.16 to 1.27; $P = 0.01$) with no heterogeneity among the studies (I2=0%, heterogeneity $P = 0.61$) (Figure 3). (Figure 2) (Figure 3)

Sensitivity analysis: No heterogeneity was observed among the included studies for the primary outcome, and thus we did not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

Secondary outcomes: Cardio-pulmonary function and hemodynamic stability were commonly used to assess the treatment efficacy of heart failure. Peak VO2 was thought to be the gold-standard indicator of functional capacity in patients with heart failure and great impairment may result in adverse outcomes [Guazzi 2005; Reddy 2018]. We performed the meta-analysis of peak VO2, systolic BP, mean BP, and heart rate to assess the efficacy of nitrite therapy.

In comparison with the control group for heart failure, nitrite therapy showed no obvious impact on peak VO2 (Std. MD=-0.19; 95% CI=-0.49 to 0.11; $P = 0.21$ (Figure 4), systolic BP (Std. MD=-3.98; 95% CI=-8.24 to 0.28; $P = 0.07$) (Figure 5), mean BP (Std. MD=-1.53; 95% CI=-3.37 to 0.31; $P = 0.10$) (Figure 6), or heart rate (Std. MD=0.40; 95% CI=-0.14 to 0.94; $P = 0.15$) (Figure 7). (Figure 4) (Figure 5) (Figure 6) (Figure 7)

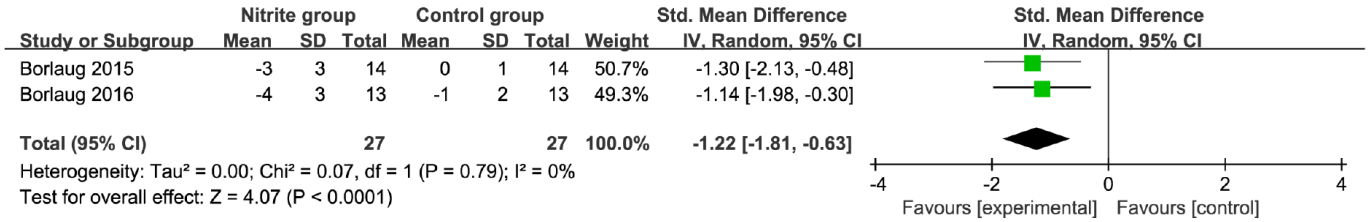

Figure 2. Forest plot for the meta-analysis of PCWP

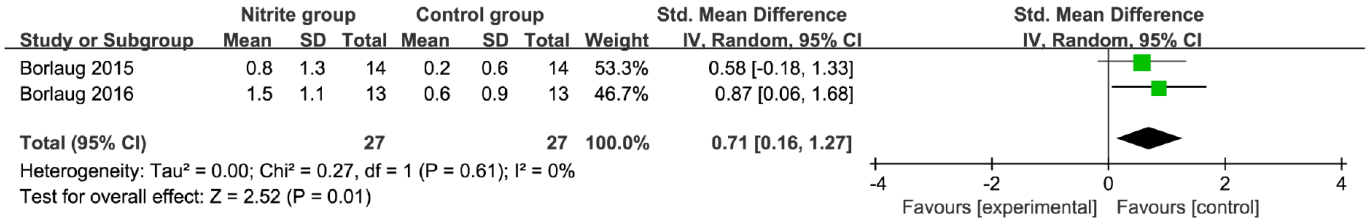

Figure 3. Forest plot for the meta-analysis of PAC

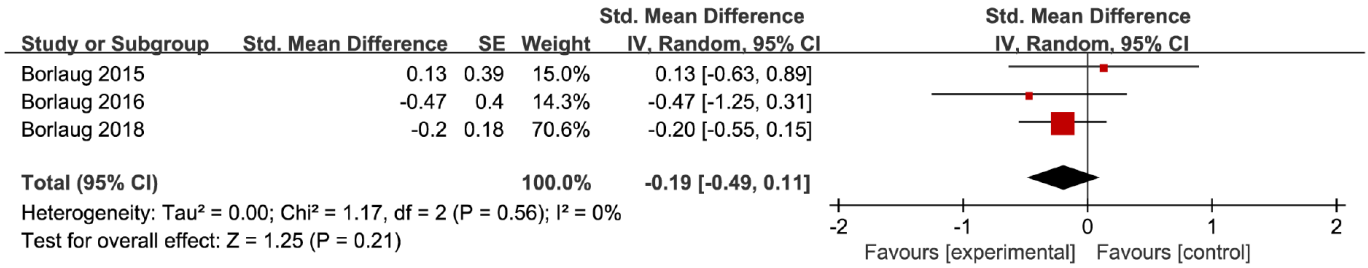

Figure 4. Forest plot for the meta-analysis of peak VO2

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DISCUSSION

The pathophysiology of heart failure is complex and involves left and right ventricular dysfunction, vascular limitations, and impairments in the periphery [Sharma 2014; Borlaug 2011; Borlaug 2014]. These patients commonly have the elevation in cardiac filling pressures at rest and with exercise [Maeder 2010; Anderson 2015]. Elevated left ventricular filling pressures results in symptoms of dyspnea, followed by pulmonary hypertension and development of right ventricular dysfunction, which may be associated with increased risk of death [Melenovsky 2014; Dorfs 2014]. Many patients with heart failure encounter the cardiac, vascular, and skeletal muscle abnormalities, which limit physical capacity [Borlaug 2010; Pryzbek 2019; van der Meer 2019]. These patients commonly have high prevalence of hypertension, coronary disease, diabetes, and sleep apnea [Ergatoudes 2019].

Treatments targeting to reduce filling pressures may be effective in these patients. Limitations in NO availability plays a key role in driving the elevations in filling pressures and pulmonary hypertension in heart failure, and agents targeting the NO/cGMP pathway represents important potential in alleviating filling pressures [Sharma 2014; Greene 2013]. In contrast to the organic nitrates, inorganic nitrite leads to no development of endothelial dysfunction [Vanderpool 2015; Lundberg 2008]. Nitrite provides a hypoxia-sensitive NO source that is preferentially active at the time of greatest need, and induces more targeted NO delivery [Borlaug 2016].

Inorganic nitrate/nitrite is believed to alleviate heart failure via targeting nitric oxide delivery during exercise [Reddy 2017]. Several studies demonstrated improvements in hemodynamics, submaximal exercise endurance, and peak VO2 using therapies targeting the inorganic nitrate/nitrite pathway [Borlaug 2015; Zamani 2015; Eggebeen 2016; Zamani 2017; Reddy 2017]. Preclinical and clinical studies revealed the benefits from inorganic nitrite and nitrate in heart failure [Borlaug 2015; Vanderpool 2015; Zamani 2015; Bhushan 2014]. Oral nitrate (delivered as beetroot juice) was found to improve exercise capacity, vasodilation, and CO reserve when given either as a single dose or as repeated doses over 1 week [Zamani 2015; Eggebeen 2016]. Intravenous nitrite was associated with reduced PCWP at rest and during exercise in hear failure [Borlaug 2015; Ormerod 2015]. Our meta-analysis confirms that nitrite therapy can remarkably reduce PCWP and improve PAC in patients with heart failure.

Measures of both maximal functional capacity (peak VO2) and volume of daily activity (accelerometry) are used to assess the efficacy of inorganic nitrite for heart failure. Reduction in

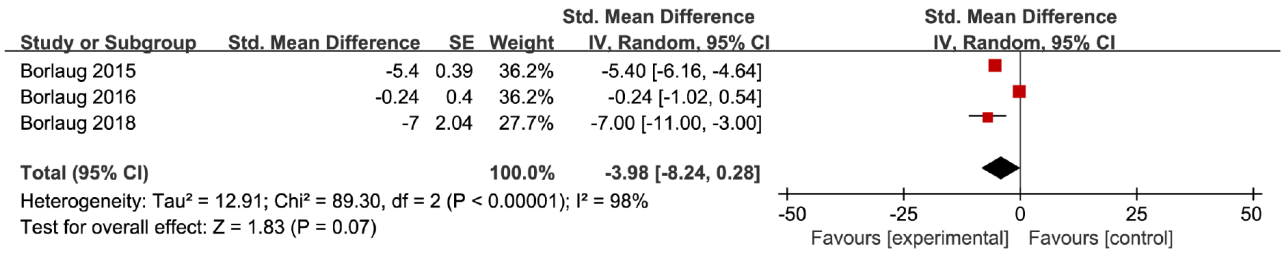

Figure 5. Forest plot for the meta-analysis of systolic BP

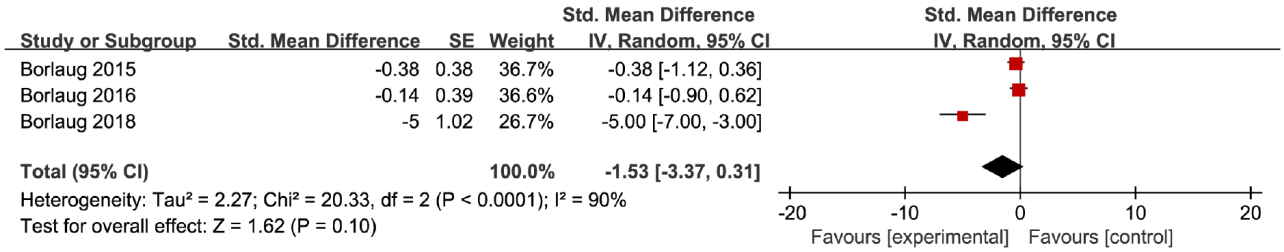

Figure 6. Forest plot for the meta-analysis of mean BP

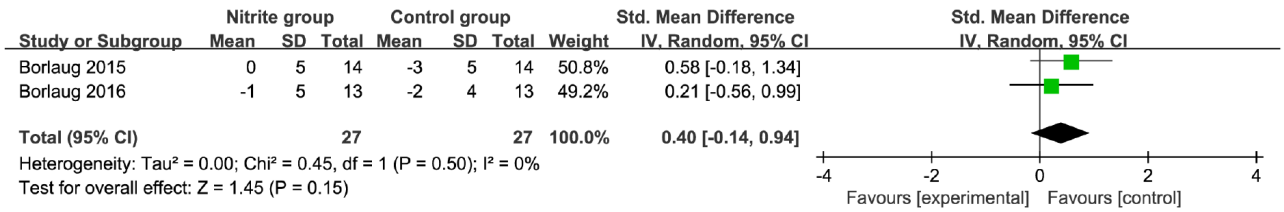

Figure 7. Forest plot for the meta-analysis of heart rate

peak VO2 indicates high cardiac filling pressures that alleviate the symptoms of dyspnea and abnormalities peripheral to the heart in the vasculature and skeletal muscle [Reddy 2018; Obokata 2018; Houstis 2018; Eisman 2018; Weiss 2017]. In this meta-analysis, there is no statistical difference of peak VO2, systolic BP, mean BP or heart rate between nitrite therapy and placebo in patients with heart failure.

In addition, inhaled nitrite at 46 mg 3 times a day for 1 week followed by 80 mg 3 times a day for 3 weeks in patients with heart failure with preserved ejection fraction reveals no obvious favorable influence on daily activity levels, quality of life, functional class, cardiac filling pressures, or N-terminal fragment of the prohormone brain natriuretic peptide levels as compared to placebo [Borlaug 2018]. Several reasons may account for the discrepant findings and bias. Firstly, nitrite therapy is administered by intranasal or intravenous infusion, which may produce different levels of efficacy. Secondly, heart failure with or without preserved ejection fraction results in different cardiac function, and preserved ejection fraction may comprise the efficacy of nitrite therapy for heart failure. Thirdly, the doses and methods of nitrite therapy is various in each RCT and may produce some bias for the pooling results.

This meta-analysis has several potential limitations. Firstly, our analysis is based on three RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, there are some discrepant findings, which may be caused by different doses and methods of nitrite therapy and various cardiac function among included RCTs. Finally, some important outcomes such as ejection fraction, mortality, and hospitalization can not be analyzed based on current studies.

CONCLUSIONS

Nitrite therapy may provide some efficacy for the treatment of heart failure.

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