META-ANALYSIS

Effect of Levosimendan on B-type Natriuretic Peptide Levels in Patients with Heart Failure: A Systematic Review and Meta-Analysis

Guiqin Liu, MS; Xianhe Lin, MD

ABSTRACT

Objective • This meta-analysis aims to evaluate the effects of levosimendan on B-type natriuretic peptide (BNP) levels in patients with decompensated heart failure and assess the efficacy and safety of levosimendan in treating left heart failure.

Methods • Randomized controlled trials (RCTs) were identified through searches in the Chinese Biomedical Literature Database (CBM), Chinese Academic Journal Full Text Database (CNKI), Wanfang Database (CECDB), VIP Chinese Scientific, PubMed, Cochrane Library, and Web of Science. Quality assessment and data extraction were performed for the included studies, and meta-analysis was conducted using Review Manager 5.2 software.

Results • The meta-analysis revealed a statistically significant difference in the regulatory effect of levosimendan on BNP levels in patients with stage III heart failure compared to the control group [OR = 2.12, 95% CI (1.22, 3.67), P = .008, I^2 = 37%, Z = 2.67]. Additionally, leosimendan showed a significant effect on BNP levels in patients with stage IV heart failure [OR = 1.88, 95% CI (1.27, 2.79), P = .002, I^2 = 0%, Z = 3.14], compensatory heart failure [OR=2.97, 95% CI (1.81, 4.86), P < .0001, I^2 = 55%, Z = 4.32], and decompensated heart failure [OR = 1.98, 95% CI (1.59, 2.47), P < .00001, I^2 = 76%, Z = 6.07].

Conclusions • Levosimendan administration demonstrated improved cardiac function and a significant reduction in plasma BNP levels in patients with decompensated heart failure. (*Altern Ther Health Med.* 2023;29(7):184-190).

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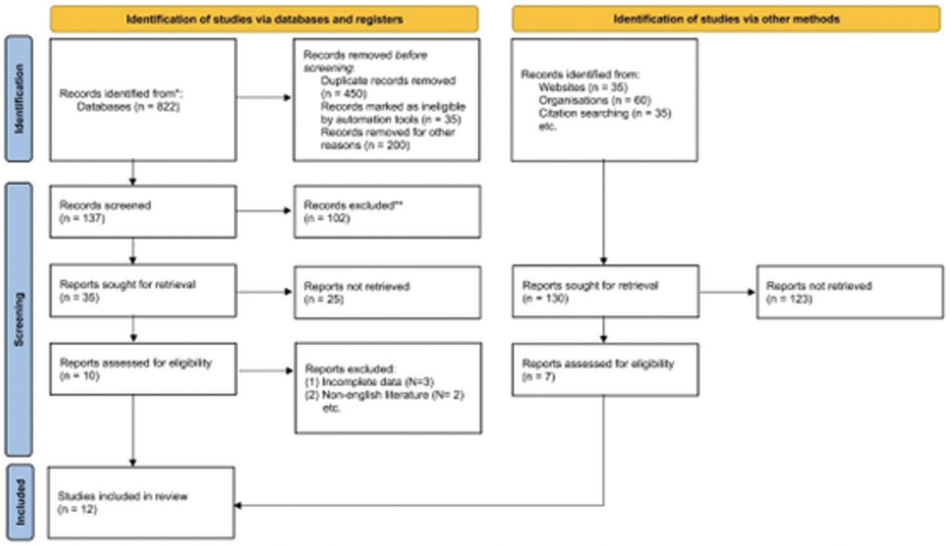
INTRODUCTION

Heart failure (HF) was recognized as an emerging epidemic in 1997 and continues to be a significant global public health concern.[1] Traditional risk factors, including hypertension, diabetes, sedentary lifestyle, hyperlipidemia, and smoking, play pivotal roles in the development of HF. These factors are either mediated by coronary disease or directly associated with HF pathogenesis.[2] It is now well-established that these factors contribute to HF through various pathways.

Levosimendan, a novel positive inotropic drug, shows promising clinical applications. It acts as a calcium sensitizer, enhancing cardiac sensitivity to calcium without increasing intracellular calcium concentration by augmenting calcium binding to troponin-C and inhibiting ATP-dependent potassium channels, levosimendan functions as both an inotrope and a vasodilator.[3] It has been employed in treating decompensated heart failure and can potentially improve cardiac function in patients undergoing cardiac surgery by replacing milrinone and dopanol tincture.[2-4]

B-type natriuretic peptide (BNP), a cardiac neurohormone, primarily influences kidney function by promoting natriuresis and diuresis. Preliminary results have shown that levosimendan can enhance myocardial contractility and reduce plasma BNP levels in patients with decompensated heart failure.[5] Heart failure represents the ultimate outcome of numerous cardiovascular diseases and stands as the leading cause of death.[6] Therapeutic approaches for HF can be categorized as either digitalis or non-digitalis interventions. Digitalis acts by inhibiting the sodium-potassium ATPase on the myocardial cell membrane. Non-digitoxin interventions include adrenal receptor agonists and phosphodiesterase inhibitors. Adrenal receptor agonists, such as dobutamine, elevate cAMP levels in the myocardium by activating adenylate cyclase.

Figure 1. PRISMA Diagram of the Literature Screening



Note: PRISMA diagram illustrating the literature selection and inclusion process flow in the meta-analysis. The diagram presents the number of studies identified, included, and excluded at each stage and the reasons for exclusion.

Phosphodiesterase inhibitors, conversely, impede cAMP breakdown by inhibiting phosphodiesterase, resulting in increased cAMP concentration in the myocardium.[7] Elevated cAMP levels exert positive inotropic and vasodilatory effects, playing a crucial role in the treatment of refractory heart failure.

As a novel calcium sensitizer, levosimendan can potentially maintain hemodynamic stability during the acute phase of heart failure, thereby facilitating comprehensive management of chronic heart failure and promoting disease stability.[8] Compensatory heart failure can manifest as a deterioration of chronic heart failure or may occur in patients without a previous history of heart failure. However, due to the limited scale of clinical trials investigating drug therapy for acute heart failure, existing studies have primarily focused on hemodynamic indicators or symptom improvement rather than long-term prognostic analysis.[9] Currently, the primary treatment strategy for acute decompensated heart failure involves the use of positive inotropic drugs, intravenous diuretics, and vasodilators to stabilize hemodynamics and alleviate symptoms. In cases where the response is inadequate, left ventricular assist devices or surgery may be considered.[10]

BNP has gained international recognition as a plasma marker for evaluating the therapeutic effectiveness of heart failure. However, the majority of studies published thus far consist of case reports, with only a limited number of systematic randomized controlled trials available. These studies often suffer from small sample sizes and inconsistent results, undermining confidence in their findings. Therefore, this meta-analysis was conducted to analyze the effect of levosimendan on BNP levels in patients with decompensated heart failure to quantitatively evaluate the efficacy and safety of levosimendan in the treatment of left heart failure.

MATERIALS AND METHODS

Study Design

The study design employed in this research is a systematic review and meta-analysis. The researchers conducted a thorough search across multiple databases to identify randomized controlled trials (RCTs) that met the inclusion criteria. Quality evaluation and data extraction were performed for the selected studies, and meta-analysis was conducted using Review Manager 5.2 software. By synthesizing the data from multiple studies, the meta-analysis provided a quantitative assessment of the efficacy and safety of levosimendan in the treatment of heart failure and its impact on BNP levels.

Search Strategy

A comprehensive search strategy was employed to retrieve relevant articles for this study. The following databases were searched: MEDLINE via PubMed, Excerpta Medica Database (EMBASE), Cochrane Cardiovascular Group, and the Chinese Biomedical Literature Disc (CBM) database. The search utilized English search terms, including "Levosimendan," "calcium sensitizer," "Heart Failure," and "B-type natriuretic peptide." See Figure 1 for an illustration of the search process.

Inclusion and Exclusion Criteria

To be included in this study, the literature had to meet the following criteria: (1) It had to be a randomized controlled trial; (2) The patients included in the study must have met the New York Heart Association (NYHA) cardiac function classification of grade III-VI; (3) The left ventricular ejection fraction (LVEF) of the patients had to be less than 35%; (4) Levosimendan was administered through intravenous (IV) infusion for a duration of 24 hours; (5) The literature provided

mean values and standard deviations for plasma B-type natriuretic peptide (BNP) levels. Patients with a history of myocardial infarction, inosine levels greater than 2.5 mg/dL, or recumbent systolic blood pressure below 95 mmHg within the last 8 weeks were excluded from the analysis.

The following criteria were used to exclude literature from the study: (1) Non-randomized controlled experimental designs; (2) In the case of two publications reporting the same data, the one published first was selected for analysis; (3) Literature that did not provide valid data for analysis; (4) Secondary publications of the same study; (5) Studies involving combined drug therapies; (6) Repetitive publications.

Literature Screening, Quality Evaluation, and Data Extraction

Two independent evaluators conducted the screening, quality evaluation, and data extraction process. Initially, the title of each piece of literature was reviewed, followed by a thorough assessment of the abstract to determine its relevance to the study's content. For randomized controlled trials meeting the inclusion criteria, the full text of the literature was carefully reviewed. Any discrepancies in literature selection between the two reviewers were resolved through group discussion. In cases where detailed data were not readily available, the authors of the studies were contacted via email or through a review of the literature references related to the particular study.

The two reviewers utilized the Jadad rating scale to independently assess the quality of 15 selected studies. This scale primarily evaluates the randomized controlled experimental design of the included literature. The evaluation criteria comprised the following: (1) Generation of random sequence ("yes" = 2, "unclear" = 1, "no" = 0); (2) Allocation concealment ("yes" = 2, "unclear" = 1, "no" = 0); (3) Blinding ("yes" = 2, "unclear" = 1, "no" = 0); (4) Withdrawals and dropouts ("yes" = 1, "no" = 0). A score of 1-3 indicates low quality, while a score of 4-7 indicates high quality.

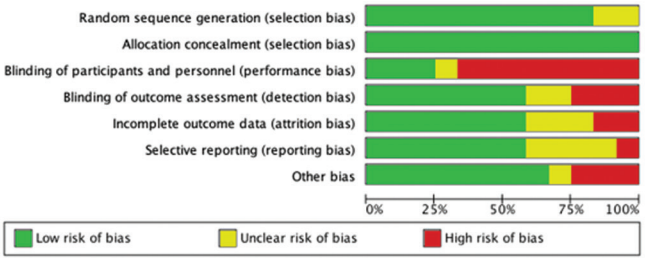
Data extraction involved obtaining information such as author details, country, Jadad score, patient demographics (age and gender), study drug dosage, number of cycles, treatment efficacy, pre-and post-treatment Hamilton Depression Rating Scale (HAMD) scores, and adverse reaction status. Following data extraction, the two evaluators compared their findings, discussed any discrepancies and made efforts to supplement missing information whenever possible.

Bias Analysis

To assess heterogeneity between studies, I^2 statistics were utilized. A value of 25%, 50%, and 75% corresponded to low, medium, and high heterogeneity, respectively. Fixed-effect models were employed to analyze the data if $I^2 < 50\%$ and the $P > .1$. Conversely, random-effects models were utilized if $I^2 > 50\%$ and the $P < .1$ based on the chi-square analysis, indicating significant study heterogeneity. Subgroup analysis was conducted to explore potential sources of heterogeneity. Sensitivity analysis was performed by systematically excluding one included literature at a time to evaluate the stability and reliability of the pooled effect values; refer to Figure 2 and Figure 3.

Figure 2. Literature Quality Evaluation Chart. **A**. Risk of bias graph: The graph presents an assessment of the risk of bias for each included study. It provides a visual representation of the distribution of bias across different domains, such as random sequence generation, allocation concealment, blinding, and completeness of outcome data. **B**. Risk of Bias Summary: The summary provides a concise overview of the risk of bias for each included study. It highlights the overall assessment of bias for each domain, allowing for a quick comparison of the quality of the studies.

A.



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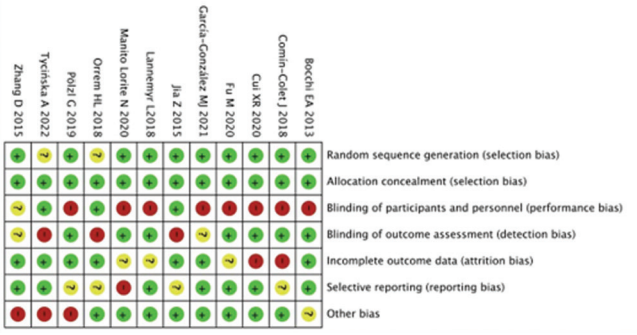


Statistical Analysis

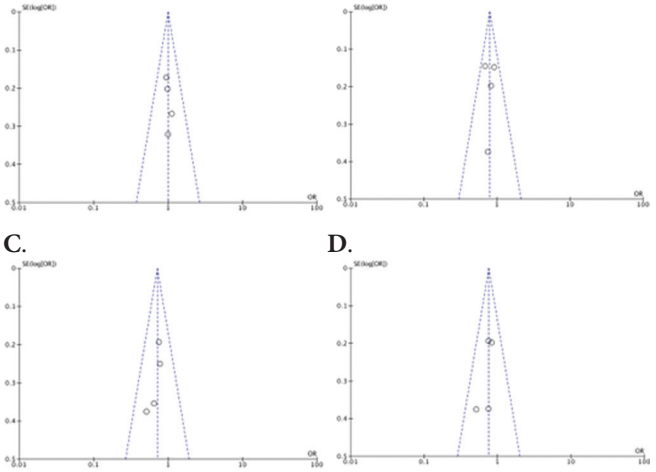
Statistical analysis was conducted using Review Manager 5.2 software provided by the Cochrane Collaboration Center. The meta-analysis used the relative risk (RR) and corresponding 95% confidence interval (CI) as statistical measures for analyzing efficacy and side effects. The chi-square test, χ^2 (with a significance level of $P < .05$), was employed, and hypothesis testing utilized the U test expressed by Z value and corresponding P value. The significance level was set at 0.05 (i.e., $P < .05$ indicated a statistically significant difference). The forest plot presented the results of the hypothesis tests. Heterogeneity was assessed using the chi-square test. $P < .10$, along with the I^2 values of 25%, 50%, and 75%, were considered indicative of low, medium, and high heterogeneity, respectively. Publication bias was evaluated using an inverted funnel plot.

RESULTS

Characteristics of Included Studies

The databases searched for this study included Pubmed, Cochrane, Web of Knowledge, Embase, CBM, CNKI, CECDB, and CQVIP. Initially, a total of relevant literature was retrieved and subjected to an initial screening. Duplicate publications and non-randomized controlled trials were excluded based on the evaluation of titles and abstracts, resulting in 35 remaining articles. A thorough review of the

Figure 3. A-D: Funnel plot of Literature Publication Bias



Note: The plot displays the effect size (such as odds ratio or standardized mean difference) on the x-axis and a measure of study precision (such as standard error or sample size) on the y-axis. The asymmetry of the funnel plot can indicate the presence of publication bias, with studies with smaller sample sizes and less precise estimates potentially missing from the plot. An asymmetric funnel plot suggests no significant publication bias, while an asymmetric plot may indicate the presence of bias.

full papers was conducted, excluding different reports of the same clinical study and literature that did not align with the study's content. Additionally, the references of relevant articles were examined to prevent any potential literature omissions. Ultimately, a total of 12 randomized controlled trials (RCTs) were included in this study.[11-22] The entire process of retrieval and screening was independently performed by two evaluators, with any discrepancies resolved through internal discussions; refer to Table 1.

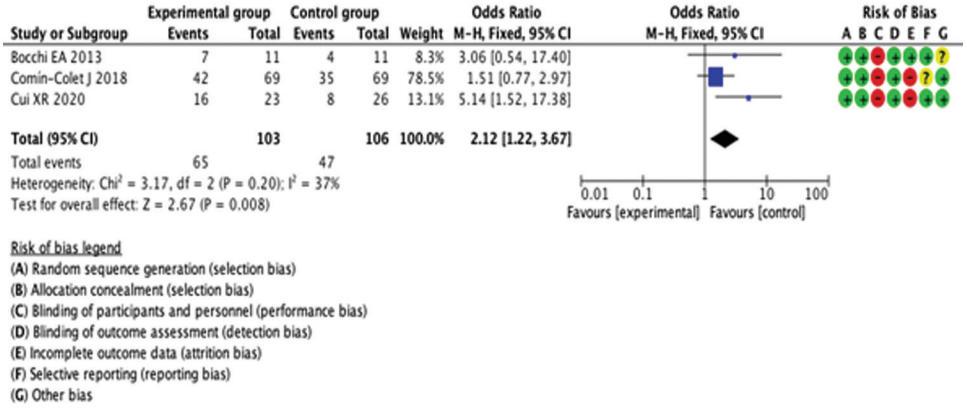
Effect of Levosimendan on BNP Levels in Stage III Heart Failure

Among the 12 included RCTs investigating the regulatory effect of levosimendan on BNP levels in stage III heart failure, a heterogeneity test was conducted, revealing small heterogeneity among the selected studies. Therefore, a meta-analysis using fixed models was performed. The forest plot representing the regulatory effect of levosimendan on BNP levels in stage III heart failure, based on three included studies, showed non-overlapping confidence intervals between the diamond and vertical lines. This finding indicated a statistically significant difference between the experimental group and the control group [OR = 2.12, 95% CI (1.22, 3.67), $P = .008$, $I^2 = 37\%$, $Z = 2.67$]. Refer to Figure 4.

Table 1. Basic clinical features of 12 included studies

Study	Age	Gender (Man)	Experimental Group	Control Group	NOS Score	Research Type
Comín-Colet et al., 2018	55.71 ± 1.2	41.25%	42/69	35/69	7	RCT
García-González et al., 2021	57.65 ± 3.4	59.12%	12/27	23/70	9	RCT
Cui et al., 2020	43.12 ± 4.5	45.72%	16/23	8/26	8	RCT
Orrem et al., 2018	47.15 ± 4.5	44.12%	45/52	21/44	8	RCT
Jia et al., 2015	42.85 ± 8.4	51.89%	70/120	50/120	8	RCT
Lannemyr et al., 2018	64.36 ± 1.2	53.45%	20/32	12/32	7	RCT
Tycińska et al., 2022	54.36 ± 1.2	56.35%	210/350	175/350	8	RCT
Pölzl et al., 2019	64.45 ± 1.5	62.45%	24/56	18/65	8	RCT
Fu et al., 2020	57.35 ± 1.2	55.66%	37/50	30/50	7	RCT
Manito Lorite et al., 2020	44.36 ± 1.4	58.84%	54/72	44/72	8	RCT
Zhang et al., 2015	61.38 ± 1.6	65.47%	168/248	102/248	7	RCT
Bocchi et al., 2013	65.36 ± 1.6	56.45%	7/11	4/11	7	RCT

Figure 4. Meta-analysis of the regulatory effect of levosimendan on BNP level of III heart failure between two groups

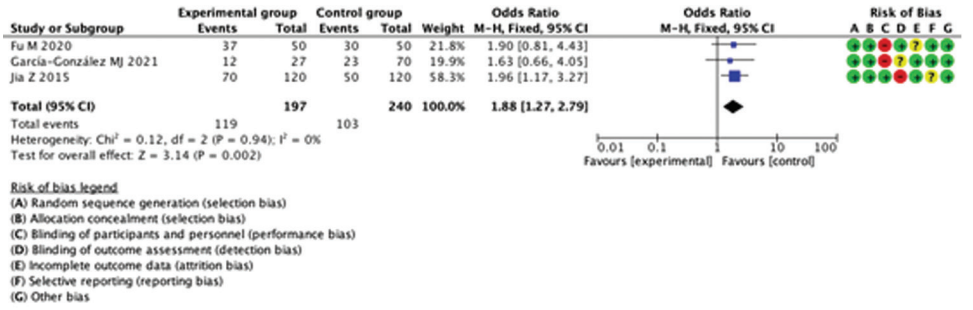


Note: The plot displays the individual studies as squares, with the size of the square representing the weight of the study in the meta-analysis. The horizontal lines represent the confidence intervals around the effect estimates, and the diamond shape represents the overall effect estimate and its confidence interval. The non-overlapping confidence intervals and their position relative to the vertical line of no effect indicate the statistical significance and direction of the findings.

Effect of Levosimendan on BNP Levels in Stage IV Heart Failure

Among the 12 included RCTs investigating the effect of levosimendan on BNP levels in stage IV heart failure, a heterogeneity test was conducted, revealing small heterogeneity among the selected studies. Therefore, a meta-analysis using fixed models was performed. The forest plot representing the effect of levosimendan on BNP levels in stage IV heart failure, based on three included studies, showed non-overlapping confidence intervals between the diamond and vertical lines. This finding indicated a statistically significant difference between the experimental group and the control group [OR = 1.88, 95% CI (1.27, 2.79), $P = .002$, $I^2 = 0\%$, $Z = 3.14$]. Refer to Figure 5.

Figure 5. Meta-analysis of the regulatory effect of levosimendan on BNP level of IV heart failure between two groups

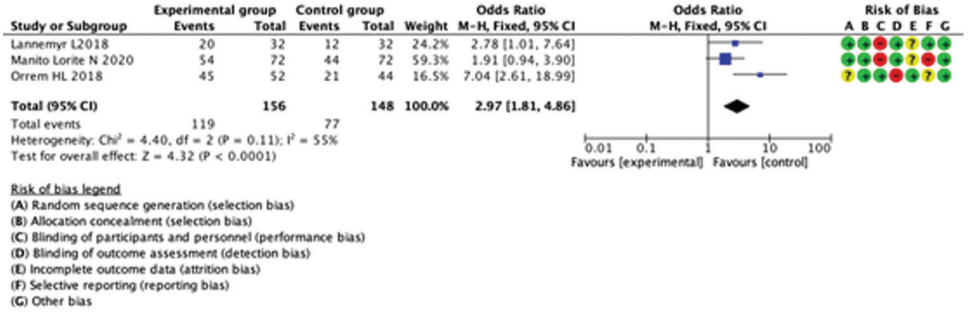


Note: In the forest plot, each square represents the findings from an individual study, with the size of the square indicating the study's weight in the analysis. The horizontal lines extending from the squares represent the confidence intervals, which provide an estimate of the precision of the effect size. The diamond-shaped symbol at the bottom represents the overall effect estimate and its corresponding confidence interval.

Effect of Levosimendan on BNP Levels in Compensatory Heart Failure

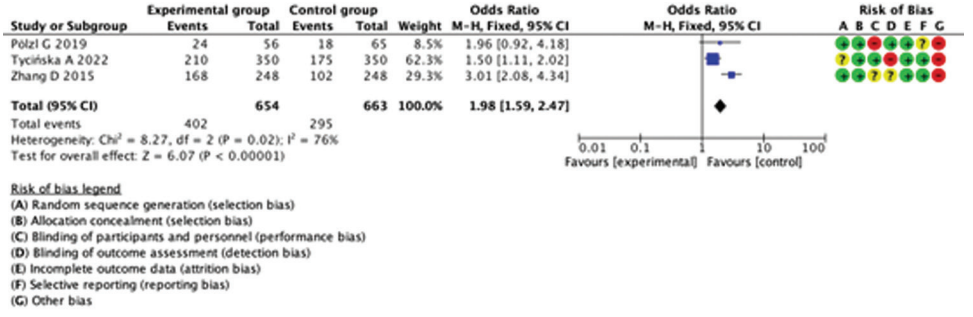
Among the 12 included RCTs investigating the effect of levosimendan on BNP levels in compensatory heart failure, a heterogeneity test was conducted and revealed small heterogeneity among the selected studies. Therefore, a meta-analysis using fixed models was performed. The forest plot representing the effect of levosimendan on BNP levels in compensatory heart failure, based on three included studies, showed non-overlapping confidence intervals between the diamond and vertical lines. This finding indicates a statistically significant difference between the experimental group and the control group [OR = 2.97, 95% CI (1.81, 4.86), $P < .0001$, $I^2 = 55\%$, $Z = 4.32$]. Refer to Figure 6 for an illustration of these findings.

Figure 6. Meta-analysis of the effect of Levosimendan on BNP level in compensatory heart failure



Note: In the forest plot, each square represents the findings from an individual study, with the size of the square indicating the study's weight in the analysis. The horizontal lines extending from the squares represent the confidence intervals, which provide an estimate of the precision of the effect size. The diamond-shaped symbol at the bottom represents the overall effect estimate and its corresponding confidence interval.

Figure 7. Meta-analysis of the effect of Levosimendan on BNP level in decompensated heart failure



Note: In the forest plot, each square represents the findings from an individual study, with the size of the square indicating the study's weight in the analysis. The horizontal lines extending from the squares represent the confidence intervals, which provide an estimate of the precision of the effect size. The diamond-shaped symbol at the bottom represents the overall effect estimate and its corresponding confidence interval.

Effect of Levosimendan on BNP Level in Decompensated Heart Failure

Among the 12 included RCTs in the effect of Leosimendan on BNP level in decompensated heart failure, a heterogeneity test was conducted, revealing small heterogeneity among the selected studies. As a result, a meta-analysis using fixed models was performed. The forest plot of the effect of Leosimendan on BNP level in decompensated heart failure, based on the analysis of three included literature, showed non-intersecting diamond and vertical lines, indicating a statistical difference between the experimental group and the control group [OR = 1.98, 95%CI (1.59, 2.47), $P < .00001$, $I^2 = 76\%$, $Z = 6.07$]. Refer to Figure 7.

DISCUSSION

Levosimendan is a calcium sensitizer that stabilizes cTnC in a conformation promoting myocardial contraction in the presence of Ca2+ and initiates its action by opening ATP-sensitive K+ channels on vascular smooth muscle.[23-25] The cardiac and vascular changes induced by levosimendan have beneficial effects on coronary blood flow, pulmonary circulation, and peripheral circulation. Studies have reported a significant increase in cardiac output with levosimendan without a concurrent increase in myocardial oxygen consumption.[26] It can be combined with ACE inhibitors and β-receptor blockers and has minimal effects on liver and kidney function, blood glucose, blood lipid, and blood routine. As reported in the literature, the main adverse reaction associated with levosimendan is hypokalemia, which can be managed by potassium supplementation.[27]

Hypokalemia can exacerbate the occurrence of premature ventricular contractions (PVCs). Therefore, electrolyte disturbances, particularly hypokalemia, should be corrected before levosimendan administration, and close monitoring of electrolyte levels should be maintained during administration.[28] Blood pressure changes should also be closely observed, as levosimendan can cause a drop in blood pressure without inducing hypoperfusion. Moreover, there are studies demonstrating that intermittent repeated use of levosimendan significantly improves heart failure with good safety profiles. The combination of levosimendan and lyophilized recombinant human brain natriuretic peptide has shown promising results in treating elderly patients with acute left heart failure. Improvement in renal function, cardiovascular function, blood gas parameters, and serum inflammatory factor levels has also been observed, indicating a significant therapeutic effect.[29-31]

Levosimendan is a valuable option for short-term hemodynamic stabilization; however, long-term drug use has been associated with an increased risk of reperfusion, cardiac arrest, and arrhythmias.[29] Therefore, there is a pressing need for a drug that can enhance myocardial contractility without increasing myocardial oxygen consumption and the occurrence of arrhythmias. As a novel calcium sensitizer, Levosimendan exerts its effects by binding to troponin C, thereby increasing the sensitivity of contractile proteins to calcium. This mechanism allows troponin C to promote myocardial contraction in the presence of calcium and also involves the opening of ATP-sensitive K+ channels on vascular smooth muscle.

Animal studies have demonstrated that levosimendan in congestive heart failure models significantly improves cardiac systolic function while not affecting diastolic function. The cardiac and vascular changes induced by levosimendan have beneficial effects on coronary blood flow, pulmonary circulation, and peripheral circulation. It has been shown to increase cardiac output and decrease pulmonary capillary wedge pressure without elevating oxygen consumption. Levosimendan can be safely used in combination with ACE inhibitors and β-receptor blockers. Treatment with levosimendan leads to a substantial reduction in B-type natriuretic peptide levels, and it does not have adverse effects on liver and kidney function, blood glucose, blood lipid levels, or blood routine parameters.[30]

Traditional positive inotropic drugs are generally unsuitable for the treatment of heart failure due to their tendency to increase myocardial oxygen consumption and peripheral vascular resistance. However, as a new-generation positive inotropic drug, levosimendan possesses unique properties that set it apart. It acts as a calcium sensitizer for myocardial contractile proteins without increasing intracellular calcium concentration in cardiac cells. This characteristic allows levosimendan to enhance myocardial contractility without raising oxygen consumption. Additionally, it opens potassium channels in smooth muscle, leading to vasodilation of the coronary arteries. The dual action of levosimendan makes it a promising therapeutic agent in the latest generation of heart failure treatments.

Study Limitations

This meta-analysis has several limitations that need to be acknowledged. Firstly, some of the retrieved literature had incomplete data or various selection indicators, which resulted in the exclusion of certain studies from the analysis. It may have introduced bias and affected the overall findings. Additionally, the passive inclusion of published research reports without considering unpublished studies could have resulted in publication bias, potentially influencing the research outcomes. It is important to consider these limitations when interpreting the results of this meta-analysis.

CONCLUSION

In conclusion, the findings of this study indicate that levosimendan holds promise as a treatment option for patients with III or IV decompensated heart failure. The administration of levosimendan was associated with improved cardiac function and a significant reduction in plasma BNP levels. These results suggest that levosimendan may have a beneficial impact on the management of advanced heart failure. Further research and clinical trials are warranted to explore its efficacy and safety in a larger patient population.

Levosimendan represents a potential therapeutic option for improving outcomes in patients with severe decompensated heart failure.

DATA AVAILABILITY

The data used to support this study is available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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