Systematic review and meta-analysis of the efficacy of olprinone and MEFV gene in treating heart failure

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ABSTRACT

Cardiovascular failure is the main cause of death in industrialized societies. The results of recent studies have shown that some mutations in the MEFV gene are common in heart failure patients. For this reason, the study of mutations and genetic factors has been of great help in the treatment of this disease, but despite this, due to the heterogeneity of clinical symptoms, multiple pathophysiological processes, and environmental genetic factors, the complete understanding of the genetic causes of this disease is very complicated. As the new generation of phosphodiesterase (PDE) III inhibitor, olprinone, the inhibition of human heart PDE III by olprinone is highly selective. It is suitable for the treatment of acute heart failure (HF) and acute cardiac insufficiency after cardiac surgery. In this study Olprinone, milrinone, PDE inhibitors, cardiac failure, and HF were selected as the search terms to retrieve articles published between January 1999 and March 2022. RevMan5.3 and Stata were employed to analyze and evaluate the risk bias of the included articles. Besides, the Q test and heterogeneity were utilized to evaluate the heterogeneity between articles. The results of this research showed No heterogeneity was found between each research group. The sensitivity (Sen) and specificity (Spe) of the two methods were compared. Olprinone showed more significant therapeutic effects than other PDE inhibitors. Besides, the therapeutic effect on the patients with HF in the two groups was obvious. The incidence of postoperative adverse reactions among the patients without relieving HF was low. The influences on urine flow of the two group's was found.

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Introduction

Vascular diseases have been proposed as the most important cause of death in developing countries, and the rate of death and death related to them is equal to the rate of death and death related to cancer. The incidence rate of coronary heart disease is approximately one-third of all vascular patients. Genetic and environmental factors or the interaction between them play an important role in the occurrence of coronary artery disease. One of the genes involved in causing heart failure is the MEFV gene (NM_000243), which is located on chromosome number 16 (16p13.3). This gene was identified in 1997 and has 10 exons (1-2). Marenostin and pyrin are two proteins encoded by the MEFV gene. These proteins are expressed in neutrophils and are involved in apoptosis, pyroptosis, and necroptosis and are effective as a negative regulator in inflammatory reactions of the body, response to bacterial infections, and heart failure (1-2).

Heart failure (HF) is the terminal stage of the development of various cardiovascular diseases. It is featured complex diseases and poor prognosis, which seriously endanger human life and health. In recent years, patients with HF become an essential component of clinical diseases with the growth of the morbidity of cardiovascular diseases year by year. Epidemiological data show that the number of current patients with HF in China reaches as high as 29.97 million, accounting for about 1/3 of the total number of patients with HF worldwide. Great progress has been made in the prevention and treatment of HF and the prevalence of HF in some regions declines in recent years. However, the prevalence of HF in developing countries still shows an apparent rising trend, which may be related to hypertension, diabetes, obesity, smoking, and other bad life habits (3-4). Although rapid progress has been made in the therapy of HF and a large number of new treatment methods are introduced, the prevalence of HF is increasing worldwide. What’s more, most patients with HF are still increasing continuously, which is even higher than that for most malignant tumors. The 1-year and 3-year mortality of patients with HF in Japan are 11.3% and 29.2%, respectively. In contrast, the 1-year mortality of patients with HF in the USA is higher, and the situation in Europe is not better. The 4-year survival rate of patients with heart disease in Europe reaches only 50%. Patients admitted to the hospital due to HF may be hospitalized for treatment again or die in the same year. Although there is no exact data on the annual mortality of HF in China, the retros-
The research on the treatment of HF by PDE inhibitor olprinone was innovatively included. The therapeutic effects of olprinone and other PDE inhibitors on HF were systematically evaluated using meta-analysis to investigate the efficacy and safety of the treatment of HF by olprinone, which provided the basis for clinical medication.

Materials and Methods

Article retrieval

The Cochrane Library, PubMed, MEDLINE, EBSCO, Science Direct, and China National Knowledge Infrastructure (CNKI) databases were searched by computers. Internationally published articles on the treatment of HF by PDE inhibitor olprinone were searched. Olprinone, milrinone, PDE inhibitors, cardiac failure, and HF were set as the search terms to retrieve the relevant articles published between January 1999 and March 2022. Those terms were randomly combined to retrieve all databases and they have adjusted appropriately according to specific databases. All retrieval strategies were determined after multiple pre-retrivals. Besides, professional journals were retrieved manually to avoid omission. All research objects in the retrieved articles must be humans.

During the retrieval process, subject words were combined with free words for multiple retrievals to harvest the needed articles. The search engine was then utilized to trace each one. RevMan5.3 (Cochrane collaboration network) was employed to assess the quality of included articles.

Inclusion and exclusion criteria

Inclusion criteria:
A. The articles on the therapy of HF by PDE inhibitor
B. The articles with the diagnosis and therapy of HF as the gold standard
C. The articles with humans as the research objects
D. The articles whose true positive, false positive, false negative, and true negative values of the treatment could be acquired
E. The articles with subjects of more than 10 cases

Exclusion criteria:
A. The articles involved treatment methods other than PDE inhibitors.
B. The articles were duplicated in literature or data.
C. The articles involved treatment methods other than PDE inhibitors.
D. The articles didn’t include sufficient data that determined the treatment indexes.

Data retrieval

Uniform Microsoft Excel (Microsoft, USA) was utilized by two professionals to screen articles, extract data, and cross-check the results. Should there be disagreement, they needed to consult with each other to settle it down. The extracted data included the general included data and information (title, the first author, and publication year), the basic features of research objects (case number, age, and gender), interventional measures (name of drugs and disease course), the key factors of bias risk evaluation (methods for randomness, whether blind method was carried out, and allocation concealment), and the effective rate of the focused outcome indexes and outcome measurement data, the incidence of adverse reactions, as well as hemodynamic indexes.

Article evaluation criteria

Article quality was assessed using the QUADAS standard recommended by Cochrane (USA). Each article was rated as satisfied, dissatisfied, or uncertain regarding the quality of the included original articles determined by each evaluation index.
Statistical methodologies

RevMan5.3 (Cochrane, USA) and Stata (Stata Corp, USA) were adopted. The odds ratio (OR) of the dichotomous variable was used as the effective index, and the mean difference (MD) of the continuous variable was used as the effective index. The point estimate and the 95% confidence interval (CI) of each effect index were offered. The heterogeneity was determined by the X2 test (test level \( \alpha = 0.1 \)). The size of heterogeneity was quantitatively assessed combined with I2. If no statistical difference was revealed by the heterogeneity between the result of each article, the fixed effect model (FEM) was adopted. If the differences in heterogeneity demonstrated statistical meaning, a randomized effect model (REM) was utilized. Besides, subgroup analysis was employed to investigate the possible source of heterogeneity. The test level \( \alpha = 0.05 \) was set for meta-analysis. Forest plots, summary receiver operating characteristic (SROC) curves, and funnel plot asymmetrical linear regression were drawn. The funnel plots with various treatment indexes were used to detect potential publication bias and implement the analysis of sensitivity (Sen).

For gene analysis, first, the MEFV gene sequence was obtained from the NCBI database. Then the exact location of this gene was determined using the UCSC database. Analyses related to the Reactome site were used to investigate autophagy mechanisms and to identify their specific targets, and UCSC and GeneCards sites were used to investigate MEFV gene exons and related mutations. Then the cellular comparison of the MEFV gene was analyzed by the Human Protein Atlas OMIM database.

Results

Mechanisms of autophagy in the MEFV gene

Autophagy mechanisms act as a platform for the assembly of Beclin, ULK1, ATG16L1, and ATG8 family members and identify specific autophagy targets (17). The MEFV gene has a positive effect on the inflammatory pathway and acts as an innate immune sensor and coordinates the initiation of autophagy by identifying the targets and assembling the autophagy apparatus. Also, the MEFV gene prevents excessive inflammation caused by IL1B and IL18 by destroying several inflammatory components including NLRP1, CASP1, and NLRP3. Exons 2 and 10 are called HOPSTOP points due to multiple mutations. In exon number 10, four major mutations occur. Codons 680 (18) and 694 (19) are called HOPSTOP codons. In exon number 2, 2 major mutations in codon 148 have been detected. The presence of multiple mutations in these exons has important effects on the function of the MEFV gene (19).

Molecular cellular functions and biological activity of the MEFV gene

Molecular functions related to the MEFV gene include membrane-associated actin binding, protein amino acid binding, glycoprotein binding, zinc binding, isoform-specific homophilic binding, and protein homopolymerization. Biological activities of the MEFV gene include the immune system process, inflammatory response, positive regulation of autophagy, negative regulation of interleukin-1 beta production, negative regulation of interleukin-12 production, response to interferon-gamma, innate immune response, negative regulation of inflammatory response, negative regulation of macrophage inflammatory protein 1 alpha production, negative regulation of cytokine production involved in the inflammatory response, negative regulation of NLRP3 inflammasome complex assembly and positive regulation of cysteine-type endopeptidase activity (20).

Article retrieval results and basic information

262 articles were harvested by database retrieval. Firstly, 46 duplicated articles and 73 disqualified articles were removed. After 38 articles were eliminated for other reasons, there were 105 remaining. Regarding abstracts and titles, 37 articles were eliminated and 68 were kept. 29 research reports and overviews were eliminated, and 39 were kept. Through full-text reading, 7 articles with undesired research types and 14 with incomplete or inaccessible treatment results were eliminated. There were 11 articles with the research objects not being humans. Finally, 7 articles were utilized for meta-analysis. Figure 1 showed the retrieval process.

Among the seven articles (21-27), the sample size of the articles with olprinone treatment was 1,287, and the sample size of the articles with other PDE inhibitors for treatment was 1,287. Additionally, the sample size of 7 included articles ranged from 10 to 951. In the 7 articles, the process of the treatment of HF by PDE inhibitors was described in detail, the changes in each index of the patients before and after treatment were recorded, and different PDE inhibitors and olprinone were compared. According to the evaluation results, 4 articles were rated level A (57.14%), 2 level B (28.6%), and 1 level C (14.3%). Tables 1 and 2 displayed the basic features of these articles. Figures 2 and 3 showed the risk bias evaluation and summary of the articles plotted by Rev-

![Figure 1. Process of article retrieval.](image-url)
Results of heterogeneity evaluation

The heterogeneity results of olprinone treatment showed that the Sen and specificity (Spe) between each article showed no heterogeneity ($I^2=0.00\%$, 0.00%). Regarding the heterogeneity of the treatment by other PDE inhibitors, Sen and Spe between each article demonstrated heterogeneity ($I^2=79.79\%. 74.83\%)$. To verify whether the data of the two methods were heterogeneous and compare the indexes of different treatment methods, REM was employed for summary analysis and SROC curve fitting.

Meta-analysis of olprinone treatment

The treatment of patients with HF by olprinone was analyzed in the seven articles. Figure 4 presented the forest plots of the Sen and Spe of a single study and a summary study on the olprinone treatment of patients with HF below. The Sen of 7 articles on olprinone treatment was performed with a heterogeneity test. $Q=0.95$, df (degree of freedom)=$6.00$, $I^2=0.00\%$, and $P=0.99$, suggesting no heterogeneity between each research group. Combined Sen was $0.88$ and $95\%$CI was $(0.86,0.91)$. The lowest Sen was $0.75$ and the lowest $95\%$CI was $(0.19,0.99)$. The highest Sen was $0.90$ and the highest $95\%$CI was $(0.55,0.99)$. Besides, the Spe of 7 articles on olprinone treatment was performed with a heterogeneity test. $Q=3.87$, df=$6.00$, $I^2=0.00\%$, and $P=0.69$, demonstrating no heterogeneity between each research group. Combined Spe was $0.90$ and $95\%$CI was $(0.88,0.92)$. The lowest Sen was $0.83$ and the $}

Man5.3.
lowest 95%CI was (0.36,0.99). The highest Sen was 0.92 and the highest 95%CI was (0.74,0.99).

In terms of hemodynamic indexes, the meta-analysis results of fixed effect models of 7 articles on olprinone treatment were shown in Figure 5 (Deek’s funnel plot). Olprinone showed a stable effect in treating patients with HF. No statistical difference was detected in the same treatment method (OR= 3.84, 95%CI (2.86, 5.16), P = 0.58). Olprinone treatment couldn’t reduce the incidence of postoperative adverse reactions among the patients with HF (OR=0.24, 95% CI(0.18, 0.33), P = 0.84), and no drastic difference was suggested in the same treatment method. A heterogeneity test was performed on the Sen of the hemodynamic index of olprinone treatment. Q=4.74, df(degree of freedom)=6.00, I2=0.00%, and P=0.58 showed no heterogeneity between each research group. Combined Sen was 0.81 and 95%CI was (0.75,0.86). The Spe of the hemodynamic index of olprinone treatment was performed with a heterogeneity test. Q=2.78, df=6.00, I2=0.00%, and P=0.84 suggested no heterogeneity between each research group. Combined Sen was 0.79 and 95%CI was (0.72,0.84).

In terms of urine flow, olprinone treatment could increase the urine flow of patients. There was a statistical difference in the same treatment method (OR= 4.00, 95%CI(2.86, 5.61), and P<0.01). The probability that olprinone treatment couldn’t increase urine flow was 44% (OR=0.44, 95% CI(0.31, 0.62), and P<0.01), which indicated considerable differences. Sen of the hemodynamic index of olprinone treatment was assessed using a heterogeneity test. Q=31.64, df=6.00, I2=67.71%, and P<0.01 indicated certain heterogeneity between each research group. Spe of the hemodynamic index of olprinone treatment was performed with a heterogeneity test. Q=99.56, df=6.00, I2=93.97%, and P<0.01, revealing substantial differences in heterogeneity between each research group.

To further observe the therapeutic effects, the treatment was analyzed comprehensively. Figure 6 was a Galbraith meta-analysis diagram. The assessment of the heterogeneity and potential abnormal values between each article suggested that the difference in heterogeneity between each article was very little with high accuracy (ACC). Figure 7 was a bivariate boxplot in which the evaluation of therapeutic effects could be obtained. The method demonstrated good Spe and Sen in treatment. Figure 8 presented SROC curves of olprinone treatment. The proximity of SROC curves to the top left corner of the plot indicated the larger area under the SROC curve and higher therapeutic Acc. Figure 9 displayed a likelihood matrix analysis. Positive likelihood ratio and negative likelihood ratio could be observed. The proportions of false negatives and false positives.
were low, while therapeutic Acc was high. All articles were
detected by Western blotting. Spe of olprinone treatment
was high and olprinone could better improve the hemo-
dynamic index. Figure 10 showed funnel asymmetrical
linear regression analysis. The random effect was utilized
to further detect the therapeutic effect. It was found that the
difference in heterogeneity between each article was little
with high Acc.

Meta-analysis of the treatment by other PDE inhibitors

In 7 included articles, the results of the treatment of pa-
tients with HF by other PDE inhibitors were analyzed. Fi-
gure 11 were the forest plots of the Sen and Spe of a single
study and summary study on the treatment of patients with
HF by other PDE inhibitors below. The Sen of 7 articles
on the treatment by other PDE inhibitors was performed
with a heterogeneity test. Q=0.29, df=6.00, I²=79.79%,
and P<0.01 suggested high heterogeneity between each
research group. Combined Sen was 0.69 and 95%CI was
(0.59, 0.78). The lowest Sen was 0.60 and 95%CI was
(0.15, 0.95). The highest Sen was 0.81 and 95%CI was
(0.77, 0.84). Besides, the Spe of 7 articles on the treatment
by other PDE inhibitors was evaluated by heterogeneity
test. Q=23.84, df=6.00, I²=74.83%, and P<0.01 showed
no heterogeneity between each research group. Combined
Sen was 0.69 and 95%CI was (0.60, 0.76). The lowest Sen
was 0.57 and 95%CI was (0.18, 0.90). The highest Sen was
0.78 and 95%CI was (0.74, 0.82).

In terms of hemodynamic index, the meta-analysis re-

results of fixed effect models of 7 articles on the treatment by
other PDE inhibitors were illustrated in Figure 12 (Deek’s
funnel plot) below. According to Figure 12, other PDE in-
hibitors showed a stable effect in treating patients with HF,
and no statistical difference was detected in the same treat-
ment method (OR= 3.61, 95%CI (2.75, 4.74), and P = 0.77).
The treatment by other PDE inhibitors couldn’t reduce the
incidence of postoperative adverse reactions among the
patients with HF (OR=0.27, 95%CI(0.21,0.35), and P =
0.97). No remarkable difference was indicated in the same
treatment method. Sen of the hemodynamic index of the
treatment by other PDE inhibitors was performed with a
heterogeneity test. Q=3.29, df=6.00, I²=0.00%, and P=0.77
indicated that no heterogeneity was detected between each
research group. Combined Sen was 0.79 and 95%CI was
(0.73,0.84). The heterogeneity test was performed on the
Spe of the hemodynamic index of the treatment by other
PDE inhibitors. Q=1.37, df=6.00, I²=0.00%, and P=0.97
suggested no heterogeneity between each research group.
Combined Spe was 0.78 and 95%CI was (0.72,0.83).

In terms of urine flow index, olprinone could enhance
patients’ urine flow. There was a statistical difference in the
same treatment method (OR= 2.56, 95%CI(1.99, 3.29), and
P<0.01). The probability that the treatment by other PDE
inhibitors couldn’t increase urine flow was 34% (OR=0.34,
95%CI(0.24, 0.49), and P<0.01), which showed significant
differences. The heterogeneity test on the Sen of the hemodynamic index of the treatment by other PDE inhibitors showed that $Q=20.71$, df $=6.00$, $I^2=48.47\%$, and $P<0.01$, indicating heterogeneity between each research group. The Spe of the hemodynamic index of the treatment by other PDE inhibitors was performed with a heterogeneity test. $Q=33.97$, df $=6.00$, $I^2=82.34\%$, and $P<0.01$ suggested that the difference in heterogeneity between each research group was remarkable.

To further observe the therapeutic effects, the treatment was analyzed comprehensively. Figure 13 was a Galbraith meta-analysis diagram. The assessment of the heterogeneity and potential abnormal values between each article suggested that the difference in heterogeneity between each article was very little with high Acc. Figure 14 was a bivariate boxplot in which the evaluation of therapeutic effects could be obtained. The method demonstrated good Spe and Sen in treatment. Figure 15 presented SROC curves of the treatment by other PDE inhibitors. The proximity of SROC curves to the top left corner of the image indicated the larger area under the SROC curve and higher therapeutic Acc. Figure 16 displayed a likelihood matrix analysis. The positive likelihood ratio and negative likelihood ratio of the data could be observed. The proportions of false negative and false positive were scattered and the therapeutic Acc was uncertain. All articles were detected by Western blotting. The Spe and Sen of the treatment by other PDE inhibitors were lower than those of olprinone treatment. No

notable difference in the improvement of the hemodynamic index was revealed between the treatment by other PDE inhibitors and olprinone treatment. Figure 17 showed funnel asymmetrical linear regression analysis. The random effect was utilized to further detect the therapeutic effect. It was found that the difference in heterogeneity between each article was little with high Acc.

Reliability analysis

The Sen was analyzed by changing analysis models. Meta-analysis showed that the summary of results with various analysis models revealed no great changes, which indicated that all involved articles demonstrated high stability. The model analysis, such as funnel asymmetrical linear regression analysis also suggested that the verification by Spe and Sen was consistent.

Discussion

Chronic HF refers to the symptom of the reduction in
cardiac output, reduce cardiac load as well as myocardial oxygen consumption, and relieve congestive HF. Besides, PDE III inhibitors can delay the further development of HF by inhibiting cytokines and inflammatory factors (33).

At present, several venous dilators with the properties of cardiotonic and vasodilator can be employed to treat HF. Among various regulators that can be administered intravenously, milrinone, olprinone, anagrelide (PDE III inhibitors), and oxymutrate (an adenylate cyclase activator) are approved for clinical application in Japan (34). Because of the role of their vasodilators, these drugs possess greater potential in improving left ventricular function and hemodynamics than strict cardiotonic drugs. They are also superior to catecholamine in terms of working efficiency and the influences on myocardial oxygen supply and demand. In addition, their immunomodulators can significantly improve rapidly deteriorated hemodynamics among patients with chronic HF caused by the downregulation of a-adrenergic receptor without involving a-adrenergic receptor as a cardiac reinforcing agent. Immune inoculant is expected to benefit the patients without catecholamine response. Some scholars research dobutamine administered to milrinone or patients with HF and compare the abilities of the two drugs to improve cardiac function. Blood norepinephrine level (no increase in left ventricular dP/dt) of dobutamine-resistant patients is remarkably higher than that of dobutamine-sensitive patients (increased left ventricular dP/dt). However, it is found that there is no significant difference in blood norepinephrine levels between milrinone-sensitive patients and milrinone-resistant patients (35). Although the influences of single therapy and the combination therapy of dobutamine and PDE III inhibitors on heart rate and mean aortic pressure demonstrate no notable differences, the combination therapy increases cardiac index as well as the amount of stroke and reduces pulmonary artery and pulmonary wedge pressure. Hence, PDE III inhibitors are very effective in improving the hemodynamics of patients without response to or resistance to catecholamine.

A total of 7 articles involving 1,287 patients were used for meta-analysis. The Sen of 7 included articles on the therapy of patients with HF by olprinone was assessed with a heterogeneity test. Q=0.95, df (degree of freedom)=6.00, I²=0.00%, and P=0.99 indicated no heterogeneity between each research group. Combined Sen was 0.88 and 95%CI was (0.86,0.91). The lowest Sen was 0.75 and 95%CI was (0.19,0.99). The highest Sen was 0.90 and 95%CI was (0.55,0.99). The Spe of 7 included articles on the therapy of patients with HF by olprinone was performed with heterogeneity test. Q=3.87, df=6.00, I²=0.00%, and P=0.69 indicated no heterogeneity between each research group. Combined Spe was 0.90 and 95%CI was (0.88,0.92). The lowest Spe was 0.83 and 95%CI was (0.36,0.99). The highest Sen was 0.92 and 95%CI was (0.74,0.99). In 7 included articles,

In 7 included articles, the Sen of the therapy of patients with HF by other PDE inhibitors was performed with heterogeneity test. Q=0.29, df (degree of freedom)=6.00, I²=79.79%, and P<0.01 indicated great heterogeneity between each research group. Combined Sen was 0.69 and 95%CI was (0.59,0.78). The lowest Sen was 0.60 and 95%CI was (0.15,0.95). The highest Sen was 0.81 and 95%CI was (0.77,0.84). The Spe of 7 articles on the therapy of patients with HF by other PDE inhibitors was performed with heterogeneity test. Q=23.84, df=6.00,
The results confirmed that the Spe and Sen of olprinone therapy were higher than those of other PDE inhibitors with better therapeutic effects on patients with HF. In terms of hemodynamics, the differences between different treatment methods were not significant. Nonetheless, heterogeneity existed between different articles in terms of urine flow. More samples and high-quality articles were needed to provide a more accurate and effective basis for clinical practice.

References


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