Efficacy and safety of nesiritide in patients with decompensated heart failure: a meta-analysis of randomised trials

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ABSTRACT

Objectives: Current evidence suggests that nesiritide may have effects on renal function and decrease the incidence of mortality. However, a clear superiority using nesiritide in terms of renal toxicity and mortality in patients with heart failure was not consistently proven by previous studies. We performed a meta-analysis of all randomised trials to obtain the best estimates of efficacy and safety of nesiritide for the initial treatment of decompensated heart failure.

Method: We performed a meta-analysis of randomised trials of nesiritide in patients with decompensated heart failure (n=38 064 patients, in 22 trials). Two reviewers independently extracted data. Data on efficacy and safety outcomes were collected. We calculated pooled relatives risk (RRs), weighted mean difference and associated 95% CIs.

Results: Compared with placebo, dobutamine and nitroglycerin, nesiritide indicated no increasing risk of total mortality. Compared with the combined control therapy, nesiritide was associated with non-significant differences in short-term mortality (RR 1.24; 95% CI 0.85 to 1.80; p=0.27), mid-term mortality (RR 0.88; 95% CI 0.60 to 1.24; p=0.42) and long-term mortality (RR 0.94; 95% CI 0.75 to 1.18; p=0.61). Nesiritide therapy increased the risk of hypotension (p<0.00 001) and bradycardia (p=0.02) when compared with control therapy. Compared with dobutamine or placebo therapy, nesiritide showed no differences in serum creatinine, blood urea nitrogen and creatinine clearance, and no risk of the need for dialysis was observed in nesiritide therapy.

Conclusions: Our findings indicated that, in patients with heart failure, nesiritide was not associated with the risk of mortality. However, it increased the risk of cardiovascular adverse events. The change of serum creatinine and creatinine clearance had no significant difference, and no risk of the need for dialysis was observed after low-dose nesiritide treatment.

INTRODUCTION

Advanced decompensated chronic heart failure (CHF) is one of the most frequent reasons for hospital admissions in patients over the age of 65 years,1 with more than one million people in the USA hospitalised each year.2 Decompensated heart failure is a complex syndrome mainly caused by left or right ventricular dysfunction rather than being a single problem of low cardiac output. It is associated with endothelial dysfunction, which contributes to the pathophysiology of the syndrome,3 4 and is also connected with increased local and systemic release of oxygen-derived free radicals that cause myocardial dysfunction in patients with this syndrome.5 Inflammatory and neurohumoral activation play a significant role in the pathophysiology of decompensated heart failure.6 Despite optimal diuretics, vasodilators and oral therapy, patients with evidence of peripheral hypoperfusion and clinical deterioration also may receive positive inotropic agents, usually milrinone or dobutamine.

Nesiritide, a vasodilator agent and recombinant human brain or B-type natriuretic peptide7 9 for the treatment of acutely
| Study         | Country and centres | Year | Blinding     | Sample size | Population                        | Intervention drug | Nesiritide bolus, µg/ kg | Nesiritide infusion, µg/µg/kg/min | Nesiritide duration, h | Control drug         | Follow-up, months | Lost to follow-up, days | Jadad score |
|--------------|---------------------|------|--------------|-------------|-----------------------------------|-------------------|--------------------------|-----------------------------------|--------------------------|----------------------|---------------------|--------------------------|-------------|
| Abraham et al | Multicentres       | 2005 | Double blind | 489         | Acutely decompensated congestive heart failure | Nesiritide        | 2                        | 0.01                              | 24                       | Nitroglycerin and placebo | Hosp 0             | 5                       |             |
| Burger et al  | Multicentres       | 2001 | Open         | 261         | Acutely decompensated congestive heart failure | Nesiritide        | 0.3                     | 0.015 and 0.03                  | UNK                      | Dobutamine           | 21 days            | 0                       | 3           |
| Burger et al  | Multicentres       | 2002 | Open         | 255         | Decompensated congestive heart failure | Nesiritide        | 0                       | 0.015 and 0.03                  | 24                       | Dobutamine           | 14 days            | 0                       | 3           |
| O’Connor et al | Multicentres      | 2011 | Double blind | 7141        | Acute heart failure | Nesiritide        | 2                       | 0.01                              | 24                       | Placebo              | 30 days            | 0                       | 5           |
| Arora et al   | USA, single centre | 2007 | UNK          | 206         | Acute decompensated heart failure | Nesiritide        | 2                       | 0.015 and 0.03                  | 24                       | Placebo              | Hosp 0             | 3                       |             |
| Silver et al  | Multicentres       | 2002 | Double blind | 261         | Decompensated heart failure | Nesiritide        | 0.3 and 0.6              | 0.015 and 0.03                  | 24                       | Dobutamine           | 6                   | 2                       | 4           |
| Witteles et al | Multicentres      | 2007 | Double blind | 75          | Acute decompensated heart failure | Nesiritide        | 2                       | 0.01                              | 48                       | Placebo              | 30 days            | 0                       | 5           |
| Aronson and Burger | Multicentres | 2002 | UNK          | 82          | Decompensated congestive heart failure | Nesiritide        | UNK                      | 0.015 and 0.03                  | 24                       | Dobutamine           | Hosp 0             | 4                       |             |
| The VMAC study | Multicentres      | 2002 | Double blind | 489         | Decompensated congestive heart failure | Nesiritide        | 1                       | 0.01                              | 24                       | Nitroglycerin and placebo | 6                   | 0                       | 5           |
| Colucci et al | Multicentres       | 2000 | Open         | 432         | Symptomatic congestive heart failure | Nesiritide        | 0.3 and 0.6              | 0.015 and 0.03                  | 3                        | Placebo              | 21 days            | 0                       | 4           |
| Chen et al    | Multicentres       | 2013 | Double blind | 360         | Acute heart failure and renal dysfunction | Nesiritide        | 0                       | 0.005                             | 24                       | Dobutamine and placebo | 180 days           | 4                       | 5           |
| Chow et al    | USA, single centre | 2011 | Open         | 89          | Acutely decompensated heart failure | Nesiritide        | 2                       | 0.01                              | 24                       | Nitroglycerin         | Hosp UNK           | 3                       |             |
| Peacock et al | Multicentres       | 2005 | Double blind | 237         | Acutely decompensated heart failure | Nesiritide        | 2                       | 0.01                              | 12                       | Placebo              | Hosp UNK           | 4                       |             |
| Peacock et al | Multicentres       | 2004 | Double blind | 61          | Acutely decompensated heart failure | Nesiritide        | 2                       | 0.01                              | 24                       | Nitroglycerin         | 6                   | 0                       | 5           |

Continued
| Study             | Year | Country and centres | Blinding       | Sample size | Population                                                                 | Intervention bolus, µg/kg | Nesiritide infusion, µg/kg/min | Nesiritide duration, h | Control drug | Follow-up, months | Lost to follow-up, days | Jadad score |
|------------------|------|---------------------|----------------|-------------|-----------------------------------------------------------------------------|---------------------------|--------------------------------|----------------------------|--------------|-----------------|------------------------|-------------|
| Peacock et al ²⁹ | 2005 | Multicentres        | Double blind   | 250         | Patients with dyspnoea at rest resulting from heart failure                 | Nesiritide                | 2                              | 0.01                       | 12           | Placebo         | 30 days                | 1           |
| Styron et al ³⁰  | 2009 | Multicentres        | UNK            | 595         | Acutely decompensated heart failure                                         | Nesiritide                | UNK                            | NA            | UNK          | Placebo         | 180 days                | 0           |
| Carroll et al ³¹  | 2007 | Multicentres        | Open           | 25 330      | Congestive heart failure                                                   | Nesiritide                | UNK                            | NA            | UNK          | Placebo         | Hosp                    | 0           |
| Yancy and Singh ³² | 2006 | Multicentres        | Open           | 138         | Advanced heart failure and renal insufficiency                             | Nesiritide                | 1 and 2                        | 0.005 and 0.01 | 14 days      | Placebo         | 3                      | 4           |
| Chow et al ³³    | 2011 | USA, single centre  | UNK            | 89          | Congenital syndrome with acute decompensated heart failure                 | Nesiritide                | 2                              | 0.01                       | 48           | Nitroglycerin   | 6                      | 0           |
| Yancy et al ³⁴   | 2004 | Multicentres        | Open           | 210         | Decompensated heart failure                                               | Nesiritide                | 1 and 2                        | 0.005 and 0.01 | 6            | Placebo         | 3                      | 0           |
| Yancy et al ³⁵   | 2008 | Multicentres        | Double blind   | 911         | Acutely decompensated heart failure                                         | Nesiritide                | 2                              | 0.01                       | 6            | Placebo         | 3                      | 5           |
| Mills et al ³⁶   | 1999 | Multicentres        | Double blind   | 103         | Decompensated heart failure                                               | Nesiritide                | 0.25, 0.5 and 1.0              | 0.015 and 0.03  | 24           | Placebo         | Hosp                    | UNK         |

Hosp, during hospitalisation; NA, not applicable; UNK, unknown.
decompensated heart failure produced primarily by the ventricular myocardium in response to volume and pressure overload, was approved by the Food and Drug Administration in 2001, and became the first new therapy for acute decompensated heart failure in 14 years.

In clinical studies, nesiritide had been found to acutely reduce pulmonary capillary wedge pressure (PCWP), systemic blood pressure, left ventricular filling pressure and systemic vascular resistance (SVR). It also increased cardiac output without direct inotropic effects, promoted diuresis by opposing the effects of endothelin 1, and improved short-term symptoms of dyspnoea and glomerular filtration rate. However, two recently published meta-analyses and one large randomised trial by O’Connor et al.16 showed that nesiritide was not associated with a worsening of renal function and the risk of mortality.

When properly applied, meta-analysis can increase the statistical power of primary endpoints, clarify disagreement among studies, and estimate effect sizes to quantify outcomes from a set of individual studies. To further clarify the role of nesiritide, we performed an updated meta-analysis of randomised trials comparing nesiritide with placebo, dobutamine, or nitroglycerin, for the initial treatment of decompensated heart failure, with particular references to the efficacy and safety.

METHODS
We attempted to identify all relevant published randomised studies comparing nesiritide with dobutamine, nitroglycerin, or placebo, for the initial treatment of decompensated heart failure. We searched between October 1950 and October 2015 from MEDLINE, between January 1980 and October 2015 from EMBASE, and between January 1976 and October 2015 from the Cochrane Library for English-language randomised controlled trials, using the terms “heart failure”, “nesiritide”, “dobutamine”, “placebo”, “nitroglycerin”, “controlled clinical trial”, “randomized controlled trial” and “random”. We also performed a manual search of references from original articles and pertinent reviews.

Study selection
The articles were independently assessed by two investigators (BG and ZW). Disagreements were resolved by consensus with a third reviewer.

Criteria for inclusions were: (1) randomised, (2) conducted in patients with heart failure, (3) compared nesiritide with dobutamine, nitroglycerin, or placebo for the initial treatment of heart failure, (4) low doses of nesiritide ($\leq 0.015 \mu g/kg/min$) and high doses of nesiritide ($>0.015 \mu g/kg/min$) and (5) use of objective methods to assess one or more clinical outcomes, including the efficacy and safety outcomes.

Outcomes
Study outcomes were analysed comparing the results from 22 trials with nesiritide versus dobutamine, nitroglycerin, placebo, or nitroglycerin.
The efficacy outcomes were PCWP, right atrial pressure (RAP), SVR, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine (SCr), blood urea nitrogen (BUN) and creatinine clearance (CrCl).

The safety outcomes were mortality, non-cardiovascular adverse events and cardiovascular adverse events. According to its follow-up duration, mortality was divided into three parts: early term (≤30 days), midterm (>30 days to 6 months), and long term (>6 months). Non-cardiovascular adverse events were nausea, headache, abdominal pain and the need for dialysis. Cardiovascular adverse events were hypotension (asymptomatic and symptomatic), ventricular extrasystole, ventricular tachycardia (sustained and non-sustained), cardiac arrest, bradyarrhythmia and angina pectoris.

### Statistical analyses

We determined pooled relative risks (RRs), weighted mean difference (WMD) and corresponding 95% CIs, for mortality, non-cardiovascular adverse events, cardiovascular adverse events, haemodynamic parameters and renal function parameters, in patients with heart failure who received nesiritide or treatment with dobutamine, nitroglycerin, or placebo. Furthermore, heterogeneity was assessed using the $\chi^2$ test and the $I^2$ measure of inconsistency. If no heterogeneity was found, meta-analysis was performed using a fixed effects model (Mantel-Haenszel method). Results obtained with a fixed effects model were also compared with those obtained with a random-effects model. All analyses were performed using Review Manager (V.5.1).

### Table 2  Measures of clinical outcomes after the therapeutic intervention

| Control group          | Outcome          | Studies, n | WMD      | 95% CI     | p Value |
|------------------------|------------------|------------|----------|------------|---------|
| High-dose nesiritide   |                  |            |          |            |         |
| Placebo                | SVR (dynes/cm²)  | 2          | -305.17  | -493.96 to -116.38 | 0.002   |
|                        | SBP (mm Hg)      | 2          | -6.87    | -11.01 to -2.73  | 0.001   |
| Dobutamine             | DBP (mm Hg)      | 1          | -6.3     | -12.39 to -0.21  | 0.04    |
|                        | SBP (mm Hg)      | 1          | -6.3     | -12.39 to -0.21  | 0.04    |
| Low-dose nesiritide    |                  |            |          |            |         |
| Placebo                | PCWP (mm Hg)     | 3          | -4.35    | -4.35 to -3.33   | <0.0001 |
|                        | SVR (dynes/cm²)  | 3          | -95.35   | -178.09 to -12.06| 0.02    |
|                        | RAP (mm Hg)      | 3          | -5.6     | -8.99 to -2.21   | 0.001   |
|                        | SCr (mg/dL)      | 1          | -0.02    | -0.11 to 0.07    | 0.66    |
|                        | BUN (mg/dL)      | 1          | -2.9     | -8.85 to 3.05    | 0.34    |
| Dobutamine             | DBP (mm Hg)      | 2          | -2.21    | -3.43 to -0.98   | 0.0004  |
| Nitroglycerin          | PCWP (mm Hg)     | 2          | -2.21    | -3.43 to -0.98   | 0.0004  |
|                        | RAP (mm Hg)      | 1          | -2.2     | -3.45 to -0.95   | 0.0005  |
|                        | SCr (mg/dL)      | 1          | -3.9     | -6.92 to -0.88   | 0.01    |
|                        | CrCl (mL/min)    | 2          | -0.04    | -0.17 to 0.08    | 0.49    |

BUN, blood urea nitrogen; CrCl, creatinine clearance; DBP, diastolic blood pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SBP, systolic blood pressure; SCr, serum creatinine; SVR, systemic vascular resistance; WMD, weighted mean difference.
RESULTS

Study selection and characteristics

There were 22 studies including 38,064 patients with decompensated heart failure in the present meta-analysis (study characteristics are listed in Table 1). 81 11 12 16 19–36 Fourteen trials were double blind, 11 16 19 22 23 25 27–29 35 36 seven were open-label trials 81 22 02 63 13 23 4 and the remaining had concealed allocation. 21 24 30 33 The dose of nesiritide varied between 0 and 2 µg/kg (as an intravenous bolus) or between 0.005 and 0.03 µg/kg/min (as a continuous infusion). Follow-up durations were ≤30 days in 14 trials, 81 21 61 9 21 23 24 26 27 31 36 37 3 months in 3 trials 32 34 35 and 6 months in 6 trials. 11 22 25 28 30 33 A PRISMA flow diagram is shown in Figure 1.

Methodological quality

We summarised the methodological quality of the Jadad score of the reported studies in Table 1. The bias assessments are shown in Figure 2 according to the risk of bias.

Meta-analysis

Efficacy outcomes

The effect of nesiritide versus nitroglycerin, dobutamine or placebo on PCWP, RAP, SVR, SCr, BUN and CrCl in patients with decompensated heart failure are shown in Table 2.

There were no significant differences between low-dose nesiritide and nitroglycerin in the efficacy outcomes of SCr (WMD, −0.04 mg/dL; 95% CI −0.17 to 0.08 mg/dL; p=0.43) and CrCl (WMD, −0.82 mL/min; 95% CI −6.95 to 5.31 mL/min; p=0.79). When we compared low-dose nesiritide with placebo, there were no consistent changes in SCr and BUN. Combining data from studies comparing high-dose nesiritide with placebo, results showed significant difference in SVR (WMD, −305.17 dynes/s/cm5; 95% CI −493.96 to −116.38 dynes/s/cm5; p=0.002).

Safety outcomes

Mortality outcomes

Forest plots of mortality outcomes are summarised in figures 3–8. Three trials contributed to the analysis on total mortality with a comparison between nesiritide and placebo (Figure 3). 16 21 23 35 Compared with placebo, nesiritide indicated no increasing risk of total mortality, with an RR of 1.04 (95% CI 0.79 to 1.38; p=0.76; figure 3). As shown in figure 4, there was no significant difference between the nesiritide and dobutamine group, regarding total mortality (RR 0.69; 95% CI 0.46 to 1.05; I²=0%; p=0.09). 12 20 22 Reanalysis with a random-effects model did not change this result (RR 0.69; 95% CI 0.46 to 1.02; p=0.89). Compared with nitroglycerin, nesiritide indicated no reduction in total mortality, with an RR of 1.10 (95% CI 0.81 to 1.49; p=0.55; figure 5). 11 28 29 Reanalysis with a random-effects model did not change this result (RR 1.10; 95% CI 0.52 to 2.34; p=0.24). Compared with the combined control therapy, nesiritide was associated with non-significant differences in short-term mortality (RR 1.24; 95% CI 0.85 to 1.80; p=0.27; figure 6), 12 16 20 21 23 26 27 30 31 mid-term mortality (RR 0.86; 95% CI 0.60 to 1.24; p=0.42; figure 7) 32 34 35 and long-term mortality (RR 0.94; 95% CI 0.75 to 1.18; p=0.61; figure 8). 11 22 26 28 30 However, no study had data regarding the safety outcome of more than 12 months.

Cardiovascular adverse events

Table 3 summarises cardiovascular adverse events identified in this meta-analysis.

In studies, nesiritide therapy increased risks of hypotension (RR 1.76; 95% CI 1.62 to 1.91; p<0.0001), asymptomatic hypotension (RR 1.72; 95% CI 1.56 to 1.90; p=0.0001), symptomatic hypotension (RR 1.59;
95% CI 1.12 to 2.27; p=0.01) and bradycardia (RR 4.46; 95% CI 1.32 to 15.02, p=0.02) in patients with heart failure compared to those using the combined control therapy. Combing data from trials comparing nesiritide therapy with the combined control therapy, the results showed significant differences in ventricular tachycardia (RR 0.43; 95% CI 0.30 to 0.62; p<0.0001), sustained ventricular tachycardia (RR 0.21; 95% CI, 0.09 to 0.49; p=0.0004), non-sustained ventricular tachycardia (RR 0.43; 95% CI 0.25 to 0.81; p=0.009) and cardiac arrest (RR 0.08; 95% CI 0.01 to 0.45; p=0.004). The pooled data revealed non-statistically significant differences in ventricular extrasystole and angina pectoris.

Non-cardiovascular adverse events

Table 3 summarises non-cardiovascular adverse events identified in this meta-analysis.

Comparing nesiritide therapy with combined control therapy, the data revealed differences in the risks of headache (RR 0.37; 95% CI 0.27 to 0.51; p<0.0001) and abdominal pain (RR 0.29; 95% CI 0.09 to 0.89, p=0.03), but not in the need for dialysis.

DISCUSSION

The objective of our meta-analysis was to assess the efficacy and safety of nesiritide, nearly 14 years after its approval for clinical use. In this meta-analysis of 22 studies involving 38,064 patients, we demonstrated no significant increase in the risks of short-term, mid-term and long-term mortality. Compared with placebo, nesiritide indicated no increasing risk of total mortality. There was no significant difference between the nesiritide and dobutamine group, regarding total mortality. Compared with nitroglycerin, nesiritide indicated no reduction in total mortality. We found that, when we compared nesiritide therapy with control therapy, nesiritide therapy was associated with an increased risk of cardiovascular adverse events, such as bradycardia and hypotension (hypotension asymptomatic and hypotension symptomatic). Compared nesiritide therapy with the combined control therapy, the pooled data revealed a non-statistically significant increase in the need for dialysis, and a significant increase in headache and abdominal pain. Importantly, in our analysis, nesiritide treatment was associated with a significant decrease in PCWP, SVR, RAP and DBP; there was no significant difference in SCR, BUN and CrCl, and none in the need for dialysis was observed.

The results of previous studies on the effect of nesiritide on survival in patients with heart failure were conflicting. Some studies showed no significant effect on mortality,11 16 31 35 and a meta-analysis of clinical trials provided a conflicting conclusion about an increased risk of mortality.15 In what concerns short-term and long-term outcomes, a meta-analysis of seven randomised controlled trials updated in 2006 reported no significant increase in the risk of short-term and long-term mortality in nesiritide-treated patients.38 An updated meta-analysis published in 2014 provided evidence that

Figure 6 Funnel plots of studies assessing the comparison of short-term mortality in nesiritide therapy versus control therapy (RR, risk ratio).

Figure 7 Funnel plots of studies assessing the comparison of mid-term mortality in nesiritide therapy versus control therapy (RR, risk ratio).
nesiritide was not associated with the risk of short-term and long-term mortality.39 Our meta-analysis included a larger number of patients, and thus had increased power. Similarly, we demonstrated that nesiritide was not associated with the risk of mortality.

To the best of our knowledge, only some previous studies showed that nesiritide had effects on haemodynamic parameters such as PCWP, SVR and SBP.81 11 In the Nesiritide Study,8 nesiritide infusion at rates of 0.015 and 0.030 µg/kg/min caused a dose-related increase in cardiac index and a dose-related decrease in PCWP, SVR and SBP. The study published by the Vasodilation in the Management of Acute CHF (VMAC) investigators in 2002 showed that nesiritide therapy reduced PCWP significantly more than standard therapy did, and a sustained effect was observed for at least 24 h.11 In the PROACTION study, Peacock et al29 demonstrated that, in the emergency department, nesiritide favourably decreased SBP of patients with elevated baseline SBP. Similarly, our meta-analysis demonstrated that nesiritide resulted in beneficial effects on haemodynamic parameters, such as decreases in SVR, SBP, DBP, PCWP and RAP. It is well known that kidney function assessment takes an essential role in patients with heart failure who have renal dysfunction. Renal insufficiency may increase risk of heart failure progression, and the pathophysiology of renal dysfunction during the process of heart failure is complex. Previous meta-analyses and studies have provided conflicting conclusions about the effect of renal function of nesiritide therapy in patients with acute decompensated heart failure. Nesiritide may be associated with a reduction in estimated glomerular filtration rate and an attenuated increase in SCr.14 23 37 40 A 2005 meta-analysis that focused on renal function of nesiritide found a factor of 1.5 increase in the rate of worsening renal function.14 However, a randomised controlled trial comparing nesiritide with placebo in patients with acute heart failure indicated that nesiritide was not associated with a worsening of renal function,16 and this result was in accord with some other previous studies.34 41 42 In addition, according to one study, nesiritide did not induce changes in urine

### Table 3  Summary risk ratios of safety outcomes with nesiritide treatment versus control treatment

| Adverse event                      | Studies, n | Nesiritide group, n | Control group, n | Risk ratio | 95% CI        | I², % |
|------------------------------------|------------|---------------------|------------------|------------|---------------|------|
| Non-cardiovascular adverse events  |            |                     |                  |            |               |      |
| Nausea                             | 2          | 347                 | 245              | 0.82       | 0.39 to 1.73  | 54   |
| Headache                           | 4          | 786                 | 666              | 0.37       | 0.27 to 0.51  | 19   |
| Abdominal pain                     | 1          | 273                 | 216              | 0.29       | 0.09 to 0.89  | NA   |
| Dialysis                           | 2          | 84                  | 80               | 0.31       | 0.01 to 7.34  | 73   |
| Cardiovascular adverse events      |            |                     |                  |            |               |      |
| Hypotension                        | 16         | 6026                | 5182             | 1.76       | 1.62 to 1.91  | 65   |
| Hypotension asymptomatic           | 10         | 5545                | 4754             | 1.72       | 1.56 to 1.90  | 54   |
| Hypotension symptomatic            | 13         | 5778                | 4915             | 1.59       | 1.12 to 2.27  | 48   |
| Ventricular extrasystole           | 2          | 451                 | 227              | 0.51       | 0.25 to 1.01  | 0    |
| Ventricular tachycardia            | 5          | 977                 | 460              | 0.43       | 0.30 to 0.62  | 32   |
| Sustained ventricular tachycardia   | 4          | 857                 | 343              | 0.21       | 0.09 to 0.49  | 25   |
| Non-sustained ventricular tachycardia | 5     | 977                 | 460              | 0.43       | 0.23 to 0.81  | 56   |
| Cardiac arrest                     | 3          | 694                 | 260              | 0.08       | 0.01 to 0.45  | 0    |
| Bradycardia                        | 4          | 927                 | 501              | 4.46       | 1.32 to 15.02 | 0    |
| Angina pectoris                    | 1          | 273                 | 216              | 0.79       | 0.23 to 2.70  | NA   |

NA, not applicable.
output, effective renal plasma flow and glomerular filtration rate. A current meta-analysis also found that nesiritide may have a dose-dependent effect on renal function in patients with acute decompensated heart failure. In the high-dose nesiritide group, nesiritide treatment was strongly associated with renal function (p=0.001). However, in standard-dose and low-dose groups, no statistical differences were observed.

Our meta-analysis is in agreement with previous studies showing that nesiritide has no significant effects on SCr, BUN and CrCl, and has no risk of the need for dialysis.

Nesiritide not only has a greater incidence of cardiovascular adverse events, but also has a higher risk of non-cardiovascular adverse events. It provides rapid effects by itself and has a distribution half-life of approximately 2 min, a mean terminal elimination half-life of approximately 18 min and multiple routes of elimination. The half-life of 18 min of nesiritide is associated with favourable adverse events in patients with heart failure. Earlier reports have described cardiovascular adverse events, including hypotension, ventricular tachycardia, cardiac arrest, bradycardia, atrial fibrillation and ventricular extrasystole. It is noteworthy that nesiritide causes a dose-dependent increase in hypotension as the most common adverse effect, usually with asymptomatic or mild symptoms. The effects of nesiritide on bradycardia and hypotensive may be associated with the autonomic nervous system. This effect is mediated by both central inhibition of sympathetic neurotransmission and inhibition of sympathetic-mediated reduction.

One study documented that the incidence of sustained ventricular tachycardia and cardiac arrest increased by approximately 12-fold, and the risk of non-sustained ventricular tachycardia increased by 1.5-fold, in the dobutamine group compared with nesiritide group. Our meta-analysis demonstrated no significant adverse events such as nausea and the need for dialysis, however, it did show adverse events for the infusion of nesiritide in patients with heart failure. However, levosimendan therapy showed higher risks of hypotension, ventricular tachycardia, cardiac arrest, bradycardia, headache and abdominal pain than control therapy did.

CONCLUSIONS

In conclusion, this meta-analysis confirmed that nesiritide therapy was not found to have significant impacts on SCr, BUN and CrCl, and no risk of the need for dialysis was observed. In contrast, nesiritide treatment was associated with significant positive effects on haemodynamic parameters. In view of the wide choice of heart failure treatment, nesiritide was not associated with the risk of mortality. Significant differences in adverse events for infusion of nesiritide in hypertension and bradycardia were observed. However, no significant difference on the need for dialysis was found.

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