Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema

Gad Cotter, Einit Metzkor, Edo Kaluski, Zwi Faigenberg, Rami Miller, Avi Simovitz, Ori Shaham, Doron Marghitay, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, Ahuva Golik

Summary

Background Nitrates and furosemide, commonly administered in the treatment of pulmonary oedema, have not been compared in a prospective clinical trial. We compared the efficacy and safety of these drugs in a randomised trial of patients with severe pulmonary oedema and oxygen saturation below 90%.

Methods Patients presenting to mobile emergency units with signs of congestive heart failure were treated with oxygen 10 L/min, intravenous furosemide 40 mg, and morphine 3 mg bolus. 110 patients were randomly assigned either to group A, who received isosorbide dinitrate (3 mg bolus administered intravenously every 5 min; n=56) or to group B, who received furosemide (80 mg bolus administered intravenously every 15 min, as well as isosorbide dinitrate 1 mg/h, increased every 10 min by 1 mg/h; n=54). Six patients were withdrawn on the basis of chest radiography results. Treatment was continued until oxygen saturation was above 96% or mean arterial blood pressure had decreased by 30% or to below 90 mm Hg. The main endpoints were death, need for mechanical ventilation, and myocardial infarction. The analyses were by intention to treat.

Findings Mechanical ventilation was required in seven (13%) of 52 group-A patients and 21 (40%) of 52 group-B patients (p=0.0041). Myocardial infarction occurred in nine (17%) and 19 (37%) patients, respectively (p=0.047). One patient in group A and three in group B died (p=0.61). One or more of these endpoints occurred in 13 (25%) and 24 (46%) patients, respectively (p=0.041).

Interpretation High-dose isosorbide dinitrate, given as repeated intravenous boluses after low-dose intravenous furosemide, is safe and effective in controlling severe pulmonary oedema. This treatment regimen is more effective than high-dose furosemide with low-dose isosorbide nitrate in terms of need for mechanical ventilation and frequency of myocardial infarction.

See Commentary page

Introduction Pulmonary oedema is a consequence of acute heart failure. This type of heart failure results from a sudden decrease in stroke volume, causing an increase in systemic vascular resistance, which in turn further reduces stroke volume, finally leading to pulmonary oedema. A combination of furosemide and nitrates is the standard treatment for pulmonary congestion. However, the effects of these two drugs have not been compared in a controlled clinical trial.

Furosemide, when administered intravenously, causes venodilatation after 15 min, thus decreasing the preload of both right and left ventricles. Furosemide also induces diuresis, which starts 30 min after administration and peaks at 1–2 h. However, furosemide also activates both the sympathetic and the renin angiotensin systems, increasing peripheral resistance. This effect might increase afterload and have a negative effect on cardiac output and stroke volume.

Nitrates are vasodilators. At low doses they induce only venodilatation, but as the dose is gradually increased they cause the arteries, including the coronary arteries, to dilate, thereby decreasing both preload and afterload.

In theory, patients with pulmonary oedema may benefit from higher doses of nitrates. Patients with heart failure have nitrate resistance, and many require high doses of nitrates for everyday treatment. Furthermore, since at high doses nitrates induce both general and coronary arteriodilatation, they reduce both preload and afterload and potentially increase cardiac output. In our study of the effects of high-dose nitrates administered as repeated intravenous boluses in the treatment of unstable angina, 33% of patients had significant pulmonary congestion that rapidly resolved on treatment with high-dose nitrates. In a preliminary study, Bosc and colleagues administered isosorbide dinitrate as an intravenous 3 mg bolus to patients with cardiogenic pulmonary oedema, with good clinical response. We therefore used this regimen in our study.

The effect of intravenous isosorbide dinitrate peaks 5 min after administration. Administration of intravenous furosemide causes dilatation after 15 min and diuresis that starts within 30 min and peaks at 1–2 h. We therefore compared the effect of isosorbide dinitrate administered intravenously as a 3 mg bolus every 5 min (combined with low-dose furosemide) with that of furosemide, administered intravenously as an 80 mg bolus every 15 min (combined with low-dose nitrates), in the treatment of severe pulmonary oedema. The use of both drugs in both treatment groups, albeit in different ratios, was dictated by restrictions imposed by the hospital and national ethics committees who approved the study design.
440 patients with signs or symptoms of pulmonary congestion
119 excluded
237 not eligible
65 mild pulmonary
congestion
54 respiratory failure
450 randomized
56 assigned to group A
54 assigned to group B
1 excluded after chest radiography
2 excluded after chest radiography
52 completed trial
52 completed trial

Figure 1: Trial profile

Methods

Patients

Patients were recruited from the Emergency Medical Services of the cities of Rishon-le-Tzion, Ramla, and Lod (total population about 250 000). All were screened by a physician and a paramedic for signs and symptoms of congestive heart failure, and all underwent electrocardiography (ECG) and chest radiography. Inclusion criteria were the presence of clinical pulmonary oedema that was confirmed by chest radiographic findings in the emergency room, and oxygen saturation of less than 90%, measured by pulse oximetry before oxygen administration, with the patient sitting. Exclusion criteria were current treatment with oral nitrates in excess of 40 mg daily, isosorbide mononitrate more than twice daily, isosorbide trinitrate more than three times daily; current treatment with oral furosemide in excess of 80 mg daily; blood pressure below 110/70 mm Hg; and previous adverse reaction to the study drugs.

Treatment protocol

Since both nitrates and furosemide are deemed essential in the treatment of acute heart failure, we were obliged, for ethical reasons, to include both of them in both treatment groups, though in different ratios. The study was designed to compare the effects of therapy with two different combinations of nitrates and furosemide administered intravenously in patients with acute heart failure, one group of patients being treated mainly with nitrates and the other mainly with furosemide.

On admission, each patient was placed in the sitting position and oxygen was administered by face mask with a rebreathing bag at a rate of 10 L/min. An intravenous line was inserted and a bolus of morphine 3 mg and furosemide 40 mg was given. Informed consent was obtained. Heart and respiratory rates, blood pressure, and oximetric oxygen saturation were obtained at baseline and every 3 min during treatment. Randomisation was done by assigning consecutive patients to one or other of the treatment groups according to their numerical order on a list that had been predetermined by lot.

In addition to this initial treatment, patients in group A (n=52) received a 3 mg bolus of isosorbide dinitrate every 5 min. Patients in group B (n=52) received an 80 mg bolus of furosemide every 15 min and isosorbide dinitrate 1 mg/h.

Results for primary outcome measures in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)

(16 μg/min) increased by 1 mg/h every 10 min. Treatment was continued in both groups until oxygen saturation increased to at least 96% or mean arterial blood pressure decreased by at least 30% or to lower than 90 mm Hg.

Intubation and mechanical ventilation were used for patients whose oxygen saturation remained below 80% for more than 20 min; those who had progressive deterioration of oxygen saturation to below 80%; and those with progressive dyspnoea, apnoea, or severe arrhythmias despite treatment. Additional morphine was administered only after intubation.

ECG examination was repeated 24 h after admission and as required during the stay in hospital. Creatine phosphokinase values were measured on admission to the emergency room and 24 h later. Echocardiography was undertaken for all patients during the hospital stay.

Outcome measures

The main outcome measures were death in hospital, need for mechanical ventilation within 12 h of admission, and development of myocardial infarction within 24 h of admission. Myocardial infarction was defined as the appearance of new Q waves on ECG or an increase in value of creatine phosphokinase above our upper normal value (150 IU/L) with an MB fraction greater than 6%. Patients were also monitored for adverse events, such as severe bradycardia or tachyarrhythmia or excessive reduction of mean blood pressure.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group A (n=52)</th>
<th>Group B (n=52)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>0·61</td>
</tr>
<tr>
<td>Required mechanical ventilation</td>
<td>7 (13%)</td>
<td>21 (40%)</td>
<td>0·0041</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9 (17%)</td>
<td>19 (37%)</td>
<td>0·047</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>13 (25%)</td>
<td>24 (46%)</td>
<td>0·041</td>
</tr>
</tbody>
</table>

Table 2: Results for primary outcome measures in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)
Apart from sinus tachycardia and mild, transient episodes of sinus bradycardia, no severe arrhythmias were recorded during drug treatment. The mean arterial blood pressure decreased from 132 (14) mm Hg to 107 (15) mm Hg (mean reduction 19% [SD 9]; p<0·0001) in group A and from 124 (24) mm Hg to 103 (19) mm Hg in group B (15% [5]; p<0·0001). The difference between the groups was not significant (p=0·26). Mean arterial blood pressure decreased excessively (>30%) in five (10%) patients in group A and in seven (13%) in group B (p=1·0), but no patient had a decrease to below 85 mm Hg or required specific treatment for hypotension. The rates of mechanical ventilation, myocardial infarction, and increase in oxygen saturation in these patients were similar to those in the rest of the respective group.

Tracheal intubation and mechanical ventilation were required in significantly fewer patients in group A than in group B (p=0·0041; table 2). Myocardial infarction also occurred in significantly fewer patients in group A than in group B (p=0·047). There was one death in group A and three in group B (p=0·61). The composite endpoint (ie, one or more of the three main outcome measures—death, mechanical ventilation, or myocardial infarction) was recorded in 13 (25%) patients in group A and in 24 (46%) in group B (p=0·041).

The improvements in all three secondary outcomes—pulse rate, respiratory rate, and oxygen saturation (figure 2)—were significantly better in group A than in group B (table 3).

Discussion

We undertook this study of patients who, before hospital admission, were treated in a mobile intensive-care unit for pulmonary oedema, to compare the safety and clinical efficacy of nitrates and furosemide in the treatment of severe pulmonary oedema in a prospective randomised investigation.

The treatment protocol was designed not only to achieve rapid resolution of pulmonary oedema, but also to avoid significant hypotension. Treatment was administered in a stepwise way under stringent blood-pressure control. This precaution was needed because, in this cohort of patients with acute heart failure, 64% had ischaemic heart disease. In such patients, significant hypotension might result in coronary hypoperfusion, which could increase the degree of ischaemia and thus lead to a further reduction of cardiac output. The mean reductions in arterial blood pressure were within the prespecified range, which is probably the preferred range for providing relief of pulmonary oedema without jeopardising coronary perfusion. Only five patients in group A and seven in group B had excessive reductions in arterial blood pressure (>30%), and even in those patients the efficacy of the treatment regimens in controlling pulmonary oedema was not reduced. Furthermore, no arrhythmic or other severe adverse

### Results

Between July 1, 1996, and June 30, 1997, 446 patients with symptoms and signs that suggested acute heart failure were screened by the Emergency Medical Services team (figure 1). We excluded 64 who had severe pulmonary oedema with respiratory failure that required immediate tracheal intubation and mechanical ventilation; 153 who had mild pulmonary congestion with oxygen saturation above 90% on admission; and 119 who met one or more of the exclusion criteria. Of the 110 patients who were randomly assigned to the two treatment groups, six were later excluded because the findings on chest radiography were not compatible with pulmonary congestion. Thus, 104 patients were finally enrolled in the study. Their baseline characteristics and current drug therapy are shown in table 1. The only significant difference between the randomised groups was in respiratory rate.

The mean dose of isosorbide dinitrate administered during treatment was 11·4 (SD 6·8) mg in group A and 1·4 (0·6) mg in group B. The mean furosemide doses were 56 (28) mg and 200 (65) mg, respectively.

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### Statistical methods

Analyses were by intention to treat. Student’s two-tailed t test was used to compare continuous variables, the paired t test to compare paired variables, and the χ² test to compare the distribution of categorical variables. Differences in heart and respiratory rates and changes in oxygen saturation over time were calculated by one-way ANOVA with repeated measures. p values lower than 0·05 were considered significant. The sample size (about 50 patients in each treatment group) was chosen to detect a 30–50% decrease in the rate of mechanical ventilation and myocardial infarction.

### Figure 2: Change in oxygen saturation during treatment in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)

Beyond the defined goal of 30% below baseline or below 90 mm Hg.

Secondary outcome measures were changes in heart rate, respiratory rate, and oxygen saturation during the first hour of treatment.

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### Table 3: Results for secondary outcome measures in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=52)</th>
<th>Group B (n=52)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Change</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>117 (18)</td>
<td>102 (15)</td>
<td>−15 (12)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>42 (17)</td>
<td>31 (14)</td>
<td>−11 (7)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>78 (8)</td>
<td>96 (7)</td>
<td>18 (8)</td>
</tr>
</tbody>
</table>

*For difference in mean change between group A and group B. †p<0·0001 for change.
events were recorded during treatment in either group. We therefore conclude that both treatment regimens were safe.

Ethical considerations dictated the use of both furosemide and isosorbide dinitrate, albeit in different ratios, in both groups of patients. However, we believe that in the final protocol we succeeded in producing two treatment groups in which one of the drugs was predominant. Patients in group A received eight times more isosorbide dinitrate than those in group B, whereas patients in group B received four times more furosemide than those in group A.

We do not believe that the administration of low-dose furosemide in the isosorbide dinitrate group (group A) and of low-dose isosorbide dinitrate in the furosemide group significantly affected the study results, for three main reasons. First, the two study groups were well matched for all relevant variables, the only difference between them being in the amount of the study drugs administered, yet the two groups differed in terms of all major and minor outcome measures. Second, most of the patients in both groups had been on background treatment with furosemide and long-acting nitrates before the study (table 1). On admission to the study, group-A patients (predominant isosorbide dinitrate) received, on average, 56 (28) mg furosemide, a dose almost identical to the background daily dose. During the first hour of treatment, group-B patients (predominant furosemide) received 1·4 (0·6) mg isosorbide dinitrate, almost identical to their background dosage (26·9 [15·1] mg nitrates over 16 h, equivalent to 1·6 mg/h). Third, nitrates have different effects at high and low doses.8 At low doses nitrates induce only venodilatation, reducing mainly the preload. At higher doses, such as those administered in group A, they induce arteriolar dilatation,10 reducing afterload and potentially increasing cardiac output. Therefore, the effect of the high doses of nitrates administered in the isosorbide dinitrate group is likely to be very different from that of the lower doses administered in the furosemide group.

We therefore believe that the two treatment regimens used in this study adequately reflect the differential effects of isosorbide dinitrate and furosemide in the treatment of severe pulmonary oedema. Substantial relief of congestive symptoms was achieved by both treatment groups. However, the effect of treatment in group A was greatly superior to that in group B (tables 2 and 3).

The regimen applied in group B (furosemide, morphine, and low-dose nitrates) is the classic approach to the treatment of pulmonary oedema. This treatment combination causes mainly venodilatation and therefore reduction of preload. Exactly how relief of pulmonary oedema is achieved by this treatment regimen is not known. Atherton and colleagues11 have suggested that the reduction of right-ventricular preload as a result of the decrease in right-ventricular volume may lead to an increase in left-ventricular volume, thereby inducing an increase in left-ventricular stroke volume. We did not measure diuretic response to treatment, since it is not our usual practice to insert urinary catheters in patients with pulmonary oedema. However, data from previous studies3–6 suggest that the diuretic effect of furosemide starts only 30 min after administration and peaks at 1–2 h. Since we assessed the effects of treatments mainly during the first 60 min, we believe that the contribution of diuresis was not significant.

Higher doses of nitrates cause arteriolar dilatation, reducing systemic peripheral resistance and thus also afterload.9 The decrease in afterload, by increasing cardiac output, might further relieve the acute heart failure, and improve pulmonary congestion.8 Accordingly, we suggest that high-dose nitrates, by causing reductions in both preload and afterload, may confer better relief of severe pulmonary oedema than furosemide.2 Our findings support this hypothesis.

Our results indicate that the administration of intravenous boluses of high-dose nitrates is safe and effective in the treatment of severe pulmonary oedema. However, the ideal dose of furosemide remains to be determined. Control of pulmonary oedema in the group that received an average furosemide dose of 200 mg (group B) was less effective than that in group A (average furosemide dose 56 mg), which implies that higher doses of furosemide are not beneficial in the treatment of severe pulmonary oedema. We should emphasise that the mean dose of furosemide used for group-A patients was higher than that specified by the treatment protocol, owing to protocol violations by physicians who felt that the patient “needed more furosemide” for the control of pulmonary oedema. Whether further reduction in furosemide dose in the treatment of severe pulmonary oedema is feasible therefore remains to be investigated.

Nitrates are traditionally used in the treatment of acute heart failure and unstable angina. They are known to be effective in reducing angina and improving left-ventricular function.12 However, their effectiveness in reducing ischaemia and in aborting myocardial infarction is controversial. We have shown previously that the intravenous administration of boluses of high-dose nitrates to patients with unstable angina reduces ischaemia clinically and on ECG.11 In that study, the rate of myocardial infarction was reduced by 35% after treatment with high-dose nitrates, but this effect was not statistically significant.

In this study, the rate of myocardial infarction showed a significant difference of 53% in favour of the group receiving high-dose nitrates. Although we did not monitor ECG changes during treatment, the results of our previous study suggest that the administration of high-dose nitrates, by causing a more rapid resolution of ischaemia, may contribute to the rapid resolution of the heart failure and the reduction in myocardial-infarction rate. We therefore believe that the intravenous administration of boluses of high-dose nitrates to patients in acute heart failure reduces rapid resolution of ischaemia, thereby reducing the rate of myocardial infarction and contributing to a more rapid resolution of congestion.

The intravenous administration of high-dose isosorbide dinitrate as repeated 3 mg boluses is more effective than furosemide treatment in controlling severe pulmonary oedema and reduces the need for mechanical ventilation. High-dose nitrate treatment may be more effective than furosemide in reducing the incidence of myocardial infarction.

Contributors
All the investigators were involved in the design of the study. In addition, Gad Cotter, Einat Metzkor, Rami Müller, Avi Simovitz, Ori Shahan, Doron Marghitay, Maya Koren, and Alex Blatt carried out the
investigations and, with Yaron Moshkovitz, collected the data; Gad Cotter, Einat Betzkor, Edo Kaluski, Zwi Faigenberg, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, and Ahuva Golik interpreted the findings; and Edo Kaluski, Zwi Faigenberg, Ronit Zaidenstein, and Ahuva Golik were responsible for safety monitoring. Gad Cotter, Einat Betzkor, Edo Kaluski, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, and Ahuva Golik wrote the paper.

References