Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: hemodynamic efficacy, clinical outcome, and economic impact

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of parenteral inotropic agents for patients with advanced decompensated congestive heart failure (CHF). The two inotropic agents compared were dobutamine (average 6.5 microg/kg per minute) and milrinone (the average dose was not reported).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with a primary diagnosis of acute exacerbation of CHF. All patients had at least a 6-month history of CHF and were in New York Heart Association (NYHA) functional class IV at the time of presentation to the clinic. Patients with systemic illness, sepsis, chronic obstructive lung disease exacerbation, and cardiogenic shock as a result of acute myocardial infarction were excluded from the study. Also excluded were patients on long-term home inotropic therapy.

Setting
The setting was secondary care. The economic study was carried out in Cleveland, USA.

Dates to which data relate
The effectiveness and resource use data were collected from July 1992 to October 1998. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a single retrospective study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
A total of 329 patients were included in the study. Of these, 269 (81.7%) patients were treated with dobutamine and 60 (18.3%) were treated with milrinone. The patients in the dobutamine group had a mean age of 61 (+/- 11) years and 207 were men. The patients in the milrinone group had a mean age of 62 (+/- 12) years and 42 were men. The patients were
allocated to the treatment arm at the discretion of the physician. There was a trend towards using milrinone in patients with a more severe degree of pulmonary hypertension.

**Study design**
This was a retrospective cohort study that was carried out in a single centre. The duration of follow-up was not reported, but it was likely to have been 3 months. No loss to follow-up was reported.

**Analysis of effectiveness**
It was unclear whether all the patients included in the study sample were accounted for at analysis. The primary health outcomes used were:

- the incidence of ventricular arrhythmias,
- acute renal failure,
- line sepsis,
- ventricular use,
- in-hospital mortality,
- home inotropic support, and
- heart transplantation listing.

The secondary outcomes were haemodynamic responses. More specifically, systolic and diastolic blood pressure, pulmonary artery systolic and diastolic pressure, pulmonary capillary wedge pressure, systemic and pulmonary vascular resistance, and cardiac output. An optimal haemodynamic response was defined as an improvement in cardiac index (>= 2.2 L/minute per m²), a decrease in pulmonary capillary wedge pressure (<= 18 mmHg), or a decrease in mean pulmonary arterial pressure (by at least 20%).

The tertiary outcomes were medical treatment of the chief exacerbation. More specifically, the use of nitroprusside, nitroglycerin, dopamine or an intra-aortic balloon pump.

There were generally no significant differences in the baseline characteristics and haemodynamic profiles of the two groups. The exception was the higher mean pulmonary arterial pressure in the milrinone group (47 mmHg) than in the dobutamine group (42 mmHg), (p<0.001).

**Effectiveness results**
There was no significant difference in the in-hospital mortality rate between the dobutamine (7.8%) and milrinone (10%) groups, or the clinical outcomes.

Both groups achieved an optimal haemodynamic response at a similar rate. However, there was a lower pulmonary artery diastolic pressure, (p<0.001), filling pressure, (p<0.001) and systemic vascular resistance, (p=0.01) in the milrinone group compared with the dobutamine group, as well as a higher cardiac output, (p=0.02).

Comparing the percentage change of each of the haemodynamic variables, there was a greater reduction in the pulmonary vascular resistance in the milrinone group, (p=0.0001), and a greater improvement in cardiac output, (p=0.03).

A total of 109 patients (40%) in the dobutamine group required parenteral nitroprusside for haemodynamic optimisation, compared with 11 patients (18%) in the milrinone group, (p<0.001).
The use of parenteral nitroglycerin, dopamine or an intra-aortic balloon pump was similar in both groups.

**Clinical conclusions**
Dobutamine-based therapy and milrinone-based therapy achieved comparable clinical efficacy.

**Measure of benefits used in the economic analysis**
Since the effectiveness analysis showed no significant differences in clinical effectiveness between the two groups, the economic analysis was based on the difference in costs only.

**Direct costs**
The cost/resource boundary of the study was not reported. Only average direct drug costs were evaluated in the cost analysis. These costs included the costs of parenteral nitroprusside, nitroglycerin and dopamine. The cost of hospitalisation was not included in the cost analysis, as the length of stay in the heart failure unit was similar in the two groups. The resource use data were estimated using actual data coming from the sample of patients involved in the effectiveness study. The source of the unit costs and the price year were not reported. Discounting was not relevant since the costs were incurred during less than 2 years. The unit costs and the quantities of resources used were not presented separately.

**Statistical analysis of costs**
The costs were presented as mean values with standard deviations. Statistical tests were carried out to compare the costs observed in the study groups.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were not performed.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The average direct drug costs were $45 (+/- 10) in the dobutamine group versus $1,855 (+/- 350) in the milrinone group.

The average direct drug costs were significantly reduced in the dobutamine group in comparison with the milrinone group, \((p<0.0001)\).

**Synthesis of costs and benefits**
The authors did not produce a summary measure that combined the costs and effectiveness, as it is likely that there was therapeutic equivalence of inotropic agents. Therefore, the economic analysis included costs only.
Authors' conclusions
Dobutamine-based therapy is an attractive approach for the treatment of decompensated advanced heart failure, achieving comparable clinical efficacy to milrinone at a significantly reduced economic cost.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparators was clear. Dobutamine-based therapy and milrinone-based therapy represented standard approaches for the treatment of decompensated CHF in the authors' setting. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a retrospective cohort study, although the authors acknowledged that a prospective randomised controlled trial would have been a more appropriate design for the study question. The authors also noted that selection bias might have occurred in the absence of random assignment, with a trend towards the use of milrinone in patients with a more severe degree of pulmonary hypertension. However, the patient groups were shown to be comparable at baseline in other haemodynamic profiles and in clinical status. The exclusion criteria were numerous. Hence, it may be difficult to generalise the authors' findings to other patients. Power calculations were not carried out and, as such, the study might not have had adequate statistical power to detect significant differences in the clinical outcomes. Similarly, the authors acknowledged that a follow-up period of longer than 3 months would have been more appropriate to identify differences in the clinical outcomes. Caution is therefore required when transferring the results of the analysis to other centres, owing to variability in standard patterns.

Validity of estimate of measure of benefit
The authors, on the grounds of equal effectiveness of the two alternatives, only considered the costs in their economic analysis. However, some secondary and tertiary outcomes showed milrinone to have a superior profile. The assumption of equivalence is therefore restricted to the primary (clinical) outcomes.

Validity of estimate of costs
Since the perspective of the study was not stated, it was not possible to assess whether all the relevant categories of costs were included in the analysis. The costs of hospitalisation and complications were not included because the length of stay and the rate of complications were similar in the two groups. Details of the unit costs, quantities of resources used, the source of the unit costs, and the price year were not reported and this limits the generalisability of the economic analysis to other settings. It is likely that the cost estimates were derived from a single centre and were specific to the study setting. Discounting was not relevant and, appropriately, was not carried out. Statistical tests of the costs were performed when the cost estimates were compared.

Other issues
The authors compared their results with those from other published studies, showing similar results. The authors did not address the issue of the generalisability of the study results to other settings. Sensitivity analyses, to account for variability in the cost or effectiveness data, were not performed. Consequently, caution should be exercised when extrapolating the study results to different settings. The results were not reported selectively and the effectiveness conclusions reflected the scope of the study. The authors reported a number of further limitations, which have been reported already.

Implications of the study
The authors recommended that long-term prospective randomised trials be performed to assess the long-term outcomes of dobutamine- and milrinone-based therapies in the treatment of decompensated CHF. The authors also recommended that milrinone-based therapy should be reserved for nonresponding patients.
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