Esmolol versus diltiazem in the treatment of postoperative atrial fibrillation/atrial flutter after open heart surgery

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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 intravenous esmolol (a beta-blocker) or intravenous diltiazem (a calcium channel blocker) following open heart or valve replacement surgery was examined. Esmolol was given as a bolus of 500 microg/kg followed by an infusion of 25 to 50 microg/kg per minute, and titrated upwards at 25 to 50 microg/kg per minute every 10 minutes, based on haemodynamic and electrocardiographic response. Patients receiving diltiazem received a bolus injection of 0.25 mg/kg over a period of 2 minutes. If the response was inadequate, a second dose of 0.35 mg/kg was given over a period of 2 minutes, 15 minutes later. Further details of maintenance infusions were provided in the paper. The controlled ventricular rate was set at less than 90 beats/minute (bpm).

Type of intervention
Primary prevention and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients over the age of 35 years who were scheduled for open heart surgery. Following surgery, patients received the intervention/comparator if they had postoperative AF/AFL with a ventricular rate greater than 100 bpm for 5 minutes and were haemodynamically stable. An extensive list of exclusion criteria was given in the paper. Patients were not excluded if they were given digoxin for postoperative rate control.

Setting
The setting was secondary care. The economic study was conducted at the Creighton University Medical Centre in the USA.

Dates to which data relate
The effectiveness data related to a period between October 1996 and February 1999. The resources and price year related to 1999.

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

Link between effectiveness and cost data
The cost data were collected prospectively using the same patients that were used in the effectiveness analysis.
Study sample
Power calculations were not reported in the determination of the sample size. Written consent was obtained from 182 patients, either before surgery or as soon after surgery as possible. The study sample comprised 30 patients, 15 of whom received esmolol and 15 who received diltiazem. The average age was 67.6 (+/- 13.6) years in the esmolol group and 72.4 (+/- 7.6) years in the diltiazem group. Eleven patients were excluded from the study because of hypotension, a slow ventricular response, or because the patient was already receiving the study medications for a different condition (e.g. hypertension).

Study design
This was a prospective, open-label, randomised controlled trial that was conducted at a single centre. The length of follow-up appears to have been until discharge from hospital. No patients were lost to follow-up. The method of randomisation was not reported.

Analysis of effectiveness
The form of analysis (intention to treat or treatment completers only) was not stated. The outcomes considered were:

- the number of treated patients converting to sinus rhythm (SR),
- the time to rate control,
- the overall time to conversion,
- the incidence of drug-induced side effects,
- the time to SR conversion at various points between 1 and 24 hours, and
- the percentage of patients who did not convert to SR but were controlled (less than 90 bpm).

The time to rate control was determined from the Creighton University Arrhythmia Monitoring Service (CREI-GARD). The length of hospital stay was also recorded. The groups were shown to be statistically similar at baseline.

Effectiveness results
During the first 6 hours of treatment, 66.6% of the esmolol group converted to SR compared with 13.3% of the diltiazem group, (p<0.05).

At 24 hours, 66.6% of the diltiazem group converted to SR compared with 80% of the esmolol group, (p non significant).

Drug-induced side effects, time to rate control (less than 90 bpm), the number of patients needing cardioversion, and length of stay were similar between the two groups.

The percentage controlled but not converted was 40% in the esmolol group and 100% in the diltiazem group, (p<0.05).

The length of hospital stay was not significantly different (14.5 +/- 9.6 days for esmolol and 9.6 +/- 3.3 days for diltiazem).

Clinical conclusions
Bearing in mind the small sample size, esmolol was more effective in converting patients to normal SR than diltiazem during the initial dosing period. However, no differences were observed at 24 hours.

Measure of benefits used in the economic analysis
The health benefit used was success in treating patients. This was derived from the effectiveness results.

**Direct costs**
Discounting was not relevant because of the short time period of analysis. The costs and the quantities were reported separately for drug administration. The costs for length of stay were based on data reported in the 'Effectiveness Results' section. The cost data were based on average wholesale prices for three generic drugs and length of hospital stay. The source of the drug costs was the Medispan PC price Chek. The esmolol drug costs per successfully treated patient were based on a dose of 94.3 microg/kg per minute, while for diltiazem the dose was 12 mg/hour. The price year was 1999.

**Statistical analysis of costs**
The data on length of stay were compared using an independent t-test, with a p-value of less than 0.05 being considered statistically significant.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was undertaken.

**Estimated benefits used in the economic analysis**
The results for successful conversions in the esmolol group were 0.67 at 6 hours and 12 hours, and 0.8 at 24 hours.

For the diltiazem group, the values were 0.13 at 6 hours, 0.53 at 12 hours, and 0.67 at 24 hours.

**Cost results**
The costs for successful conversions in the esmolol group were $169.16 at 6 hours, $253.74 at 12 hours, and $442.9 at 24 hours.

For the diltiazem group, the values were $58.14 at 6 hours, $116.28 at 12 hours, and $174.42 at 24 hours.

**Synthesis of costs and benefits**
The cost per successful conversions in the esmolol group was $253.61 at 6 hours, $380 at 12 hours, and $528.63 at 24 hours.

For the diltiazem group, the values were $434.14 at 6 hours, $219.39 at 12 hours, and $261.50 at 24 hours.

**Authors' conclusions**
The authors concluded that, although this was a small-scale study, the results suggest that esmolol is more cost-effective in converting patients to normal sinus rhythm (SR) than diltiazem during the initial dosing period. However, diltiazem is more cost-effective in the period 6- to 24-hour period. No significant differences in effectiveness occur after 24 hours.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the alternative health technologies was clearly presented. The authors noted that the absence of a placebo control arm meant that both esmolol and diltiazem were associated with high conversion rates. However, they pointed out that it would be ethically unacceptable to randomly assign patients to placebo in the presence of potentially serious tachyarrhythmia. You should decide if these technologies apply to your own setting.

Validity of estimate of measure of effectiveness
The study design chosen, a randomised controlled trial, could potentially be expected to have high validity in terms of eliminating bias and confounding. However, the authors noted some threats to the internal validity. These were the small sample size, the open-label design, the lack of a placebo arm, and the fact that patients with moderate to severe left ventricular dysfunction were not included in the analysis.

Validity of estimate of measure of benefit
The measure of benefit used in the economic analysis was appropriate, but it was specific to the intervention and patient domain, thus making cross-programme comparisons problematic. The use of a utility outcome measure such as the quality-adjusted life-year, if feasible, would have facilitated this.

Validity of estimate of costs
Although the small sample size hinders the reliability of the cost results, a number of good feature were in evidence. For example, the reporting of the costs and quantities separately (which enhances the generalisability of the results), the fact that the price year was given, and the reporting of the sources of the unit costs. The costs reflected the chosen perspective of the study (i.e. the hospital). Discounting was appropriately not conducted because of the short period of analysis (less than one year).

Other issues
The authors noted that this was the first cost-effectiveness analysis of the two drugs analysed, therefore no direct comparisons with the results of other studies were made. However, references were made to another study that compared esmolol with diltiazem in patients without heart disease who had postoperative supraventricular arrhythmias, the results being similar to those of the present study. The issue of generalisability was not discussed and, given the caveats associated with the analysis, it is likely that this feature of the study is low. The authors clearly outlined the limitations of their findings and indicated how further studies in this area could be improved.

Implications of the study
The findings of the study, in terms of clinical practice, suggested that esmolol is more cost-effective in converting patients to normal SR than diltiazem during the initial dosing period, although no significant differences in effectiveness exist after 24 hours. The authors indicated that additional studies are needed to determine the optimal drug in this patient domain.

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