Remifentanil, fentanyl, and cardiac surgery: a double-blinded, randomized, controlled trial of costs and outcomes


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
Three treatment strategies for patients undergoing elective coronary artery bypass graft (CABG) were compared. The strategies were remifentanil infusion at 0.83 microg/kg per minute, fentanyl bolus small dose (12 microg/kg) and fentanyl bolus moderate dose (24 microg/kg). All the patients continued with their usual medication until the time of the operation. In addition, they all received a standard premedication of oral temazepam (10 mg), intramuscular morphine (5 mg) and oxygen delivered via a face mask (5 L/minute).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised elective CABG patients aged younger than 75 years. Patients were excluded if they weighed more than 100 kg, were allergic to trial medications, were considered at very high risk (Tu score > 9), or had uncontrolled hyper- or hypotension. Other criteria for exclusion were congestive cardiac failure or an ejection fraction of less than 25%, atrioventricular or left bundle branch block detected on the preoperative electrocardiogram, and a pacemaker in situ.

Setting
The setting was secondary care. The economic study was carried out in Victoria, Australia.

Dates to which data relate
The dates to which the effectiveness evidence and resource use data related were not reported. The prices used were from 1999-2000.

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

Link between effectiveness and cost data
The same patients provided both the cost and effectiveness data.

Study sample
A preliminary estimate of sample size was 25 patients per group. This was based on requiring a Type I error of 0.05 and
a Type II error of 0.20 for an expected 30% reduction in time to tracheal extubation after surgery. All patients who met the inclusion criteria were initially enrolled in the study. Eighty-seven patients were included in the study, of which 10 were subsequently excluded. One patient withdrew their consent before surgery, 2 patients had their surgery deferred, and 7 patients failed to receive the correct allocated study medication. In the end, 77 patients were considered in the analysis. Of these, 29 patients received remifentanil (group R), 24 received low-dose fentanyl (group FLD) and 24 received moderate-dose fentanyl (FMD). The mean age of the patients was 64 years in group R, 61 years in group FLD and 62 years in group FMD. The numbers of males in the three groups were, respectively, 25 (group R), 20 (group FLD) and 18 (group FMD). All the patients were stratified into high risk (Tu score 2 - 6) and low risk (Tu score < 2) to ensure equality of risk between the three groups.

Study design
This was a double-blinded, randomised controlled trial (RCT). The patients were treated in a single centre and were followed up until hospital discharge.

Analysis of effectiveness
The basis of the analysis was intention to treat. The primary health outcomes used were time to tracheal extubation and the length of hospital stay. The secondary health outcomes were:

the incidence of postoperative stroke,
the incidence of myocardial infarction,
the rate of hypertension,
the rate of hypotension,
tachycardia,
bradycardia,
the rate of vasoconstrictor requirements,
the rate of inotropic support, and
cardiac pacing requirements.

The groups were shown to be comparable at baseline.

Effectiveness results
The time to tracheal extubation was 7.3 hours (interquartile range, IQR: 5.0 - 12.8) for group R, 6.5 (IQR: 4.1 - 7.8) for group FLD and 9.7 (IQR: 6.1 - 16.0) for group FMD, (p=0.025). The statistical analysis showed p-values of 0.14 for group R versus group FLD, 0.30 for group R versus group FMD, and 0.008 for group FLD versus group FMD.

The length of hospital stay was 4.9 (standard deviation, SD=2.1) days for group R, 6.8 (SD=2.0) days for group FLD and 5.0 (SD=2.0) days for group FMD, (p=0.03).

One patient in the FLD group had a postoperative stroke.

Three patients in the FLD group had myocardial infarction, (p=0.032).

The incidence of hypertension was 2 (7%) in group R, 10 (42%) in group FLD and 9 (39%) in group FMD, (p=0.005). The statistical analysis showed p-values of 0.003 for group R versus group FLD, 0.005 for group R versus group FMD, and 0.86 for group FLD versus group FMD.
The incidence of hypotension was 19 (66%) in group R, 6 (25%) in group FLD and 7 (30%) in group FMD, (p=0.006). The statistical analysis showed p-values of 0.003 for group R versus group FLD, 0.012 for group R versus group FMD, and 0.68 for group FLD versus group FMD.

There was a concomitant increase in vasoconstrictor requirement, (p<0.0005), but no difference in inotropic support, (p=0.96) or cardiac pacing requirement, (p=0.76).

Urinary cortisol excretion was significantly smaller, (p<0.0005) and urine flow was larger, (p=0.017) in group R.

The groups had similar rates of intraoperative myocardial ischaemia, (p=0.13).

Clinical conclusions
Remifentanil did not produce a shorter time to extubation in comparison with the two dosages of fentanyl used in the study. Remifentanil produced fewer episodes of hypertension but more episodes of hypotension. The lower dosage of fentanyl seemed to be associated with a higher risk of myocardial infarction.

Measure of benefits used in the economic analysis
No summary measure of benefit was produced. In effect, the authors carried out a cost-consequences analysis.

Direct costs
No discounting was carried out as the costs were incurred during less than 2 years. The costs were estimated using actual data available for 76 patients, which were obtained from hospital data sources. The total hospital costs were available from the hospital's clinical costing system for 51 patients (those treated after July 1999). For the remaining 25 patients, the costs were estimated using utilisation data from the admission transfer system in conjunction with mean unit costs from the later 51 patients. The costs were collected under the categories of operating theatre, intensive care unit, ward nursing, pharmacy, imaging, pathology, and "other" (which included allied health and medical). The costs of the operating theatre and cardiothoracic intensive care unit were estimated using a model that used information on the length of stay and operating theatre drug administration. The quantities and the costs were not analysed separately. The price year used was 1999-2000.

Statistical analysis of costs
No statistical analysis of the costs was carried out.

Indirect Costs
No indirect costs were calculated.

Currency
Australian dollars (Aus$).

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The authors reported the median costs. These were A$14,499 (IQR: 13,437 - 15,972) for group R, A$15,374 (IQR: 12,498 - 18,302) for group FLD and A$14,310 (IQR: 12,621 - 16,018) for group FMD, (p=0.61).

The authors then excluded three outliers and reported the mean costs as A$14,499 (SD=2,377) for group R, A$15,736 (SD=4,232) for group FLD and A$14,634 (SD=3,374) for group FMD, (p=0.26).

The costs for the duration of the hospital stay were calculated. These included the costs of adverse effects.

**Synthesis of costs and benefits**

The costs and benefits were not combined as the study was a cost-consequences analysis.

**Authors’ conclusions**

The aim of the study was to assess the effects of three anaesthetic regimens on the time to tracheal extubation. It did not show that remifentanil (0.83 microg/kg) was associated with a statistically significant reduction in this time in comparison with fentanyl (12 and 24 microg/kg). However, it was associated with fewer episodes of hypertension, though more episodes of hypotension. The authors pointed out that there were no statistically significant differences between the groups in terms of the costs they reported, which did not show the effect of three high cost outliers.

**CRD COMMENTARY - Selection of comparators**

The choice of the comparators, the two doses of fentanyl, was justified in that they represented current cardiac anaesthetic practice.

**Validity of estimate of measure of effectiveness**

The source of the effectiveness data was a single study, a randomised double-blinded trial, which was appropriate for the study question. The study sample was described as being typical of current cardiac surgical practice. The patients’ baseline characteristics were reported and were described as being similar, but no statistical tests were reported. Although many aspects of the effectiveness analysis were handled credibly, the authors appeared uncertain as to how much importance should be attached to outcomes other than the time to tracheal extubation, such as myocardial ischaemia and myocardial infarction.

**Validity of estimate of measure of benefit**

The authors did not derive a summary measure of health benefit. The health benefits are therefore those associated with the effectiveness outcomes.

**Validity of estimate of costs**

All the categories of cost relevant to the perspective adopted (i.e. that of the hospital) appear to have been included. However, the costs were not reported separately from the quantities and this limits the usefulness of the results to decision-makers in other settings. In addition, the authors did not report cost results that included the effect of the three high cost outliers, which again limits the usefulness of the results. There was a discrepancy between the tabulated results and the text which stated that relevant costs were given with and without outliers. The resource use quantities were taken from a single study, while the prices were taken from the authors’ setting. No other sources were used. No statistical or other analyses of the quantities or prices were undertaken. These facts limit the interpretation of the results. The price year was reported, which will ease any possible inflation exercises.

**Other issues**

The authors made appropriate comparisons of their results with the findings from other studies. However, the issue of generalisability to other settings was not addressed. The authors presented their cost results selectively as they did not include the effect of the high cost outliers on the mean costs. The authors acknowledged certain limitations of their
study. First, that it was not powered to detect differences in some variables such as myocardial ischaemia. Second, the sample size was not large enough to arrive at definite conclusions regarding cost-differences.

**Implications of the study**
The authors suggested that remifentanil has advantages in effectiveness over low-dose fentanyl in terms of hypertension, myocardial ischaemia and myocardial infarction, and neurohumoral stress ablation. The only disadvantages are associated with hypotension and a longer time to tracheal extubation. When compared with medium-dose fentanyl, there is a shorter time to tracheal extubation and an advantage in other variables apart from hypotension. The costs were not shown to be higher for remifentanil and were lower than low-dose fentanyl, but these cost comparisons excluded the effect of high cost outliers. The authors recommended that further research should involve a larger sample size, and should include the effects of the cost data for all patients.

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