Comparison of clinical and economic outcomes of two antibiotic prophylaxis regimens for sternal wound infection in high-risk patients following coronary artery bypass grafting surgery: a prospective randomised double-blind controlled trial


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 study examined two antibiotic prophylaxis regimens for patients undergoing coronary artery bypass grafting (CABG) who were at high risk of sternal wound infection (SWI).

Prophylaxis 1 was perioperative antibiotic prophylaxis with cefuroxime. This comprised 1.5 g cefuroxime given on induction, 750 mg coinciding with the reversal of anticoagulation with protamine, and two doses of 750 mg at 8 and 16 hours postoperatively (usual care).

Prophylaxis 2 consisted of rifampicin, 600 mg orally with the pre-medication and 1 hour preoperatively, and then gentamicin 2 mg/kg and vancomycin 15 mg/kg after induction of anaesthesia. A further three doses of vancomycin 7.5 mg/kg at 12-hour intervals were given postoperatively (new therapy).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients scheduled to undergo median sternotomy for primary isolated CABG, with at least one internal thoracic artery and having one or more of the following three risk factors: obesity (defined as a body mass index >30 kg/m2), diabetes mellitus, or use of the other internal thoracic artery, so that the patient undergoes bilateral internal thoracic artery grafts. Patients were excluded if they were allergic to penicillin or the study drugs, if they were taking antibiotics in the week before surgery for any reason, and if they had a high serum creatinine (>180 micromol/L) preoperatively.

Setting
The setting was a hospital. The economic study was carried out in the UK.

Dates to which data relate
The clinical and economic data were gathered between June 2003 and May 2004. The price year was not reported.

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the analysis of effectiveness.
Study sample
Power calculations were performed in the preliminary phase of the study. These suggested a total recruitment of 332 patients on the basis of the expected reduction of SWIs. Of the 486 patients undergoing elective primary isolated CABG at the authors' institution over the study period, 244 were eligible for inclusion (high-risk patients) but only 201 were enrolled (the reasons for exclusion were extensively reported). Ninety-five patients (mean age 62.9 +/- 10.2 years; 17.9% women) were included in the intervention group (new therapy) but only 87 were evaluated in the base-case analysis. One hundred and six patients (mean age 65.6 +/- 8.3 years; 17.9% women) were included in the control group (usual care) but only 99 were evaluated in the base-case analysis.

Study design
This was a prospective, randomised, double-blind, controlled clinical trial that was carried out at a single institution. Randomisation was based on a computerised random number generator. The length of follow-up was 90 days. Routine follow-up at 6 weeks included blinded assessment of the sternal wound. Surveillance was completed at 90 days with a follow-up by telephone. No patient was lost to follow-up. However, 8 patients in the intervention group did not receive the allocated prophylaxis (3 had their operation changed and 5 had a protocol violation), while 5 patients in the control group were not considered further (1 had their operation changed and 4 had a protocol violation). Two further patients in the control group were excluded from the basic analysis because of early death (less than 1 week postoperative). Both the patients and all staff involved in the clinical trial were blinded to the antibiotic regimen used.

Analysis of effectiveness
The primary clinical end point was the incidence of SWI, defined as the presence of wound infection and/or positive blood cultures and/or positive swab cultures over a 90-day period after the index surgery. The secondary outcomes were:

- the rate of 30-day infection,
- the type of wounds (superficial, deep, or organ space),
- sternal surgical debridement,
- harvest site infection,
- infection-related mortality,
- all-cause mortality,
- postoperative renal dysfunction,
- postoperative renal replacement, and
- postoperative hospital stay.

The base-case analysis of the clinical end points was conducted on the basis of treatment completers only (TCO). However, an intention to treat (ITT) analysis was also performed. A univariate hierarchical logistic regression analysis was also used to accommodate the clustering of outcomes for individual surgeons and to calculate the unadjusted odds ratio and 95% confidence intervals (CIs) between the two study groups. At baseline, the patient groups were comparable in all clinical and demographic factors.

Effectiveness results
In the TCO analysis, the rate of SWIs at 90 days was 9.2% in the intervention group and 25.2% in the control group, (p=0.004). This corresponded to a risk difference of 15% (95% CI: 4 to 26).

The reduction in infection for the intervention group was seen across all grades of infection in both the superficial...
(11.1% versus 4.6; p=0.104) and deep categories (8.1% versus 2.3%; p=0.156), being significant in combined deep or organ-space category (14.1% and 4.6%; p=0.028). This resulted in a significant reduction in the need for surgical interventions (debridement, vacuum therapy or pectoralis flap construction) from 19.2% to 4.5%, (p=0.003), and a significant reduction in readmissions due to SWI after hospital discharge from 11.1% to 3.4%, (p=0.048).

Other clinical outcomes did not differ significantly between the groups, although the intervention group showed generally better results. In particular, the infection rates at 30 days were 12.1% in the control group and 4.6% in the study group, (p=0.068). Similar conclusions were achieved in the ITT analysis.

The multilevel hierarchical regression analysis showed no difference between surgeons.

**Clinical conclusions**

The new prophylaxis regimen led to a significant reduction in the rate of SWIs in comparison with the conventional prophylactic strategy, without adversely affecting other clinical end points.

**Measure of benefits used in the economic analysis**

The health outcomes were left disaggregated and no summary benefit measure was used. In effect, a cost-consequences analysis was performed.

**Direct costs**

The perspective adopted in the study was not stated clearly, although most of the costs were incurred by the hospital. Only the costs associated with antibiotics and postoperative hospital care were considered. The hospital costs included hospital stay and intensive therapy unit stay due to the infection episode, the use of vacuum therapy, surgical procedures including sternal wound debridement and pectoralis flap reconstruction, microbiology costs and attendance at the outpatient wound clinic. The unit costs were presented only for the drugs. Other unit costs and quantities of resources used were not presented. Resource use was based on data prospectively gathered from the sample of patients included in the effectiveness study. The costs came from the hospital accounting system. Discounting was not relevant given the short time horizon of the analysis. The price year was not reported.

**Statistical analysis of costs**

The costs were presented as mean (median) values and interquartile ranges. Standard statistical analyses were carried out to test the statistical significance of differences in the costs.

**Indirect Costs**

Productivity costs were not considered.

**Currency**

US dollars ($). Some data were also reported in UK pounds sterling (£) and euros (EUR), but no conversion rate was explicitly provided.

**Sensitivity analysis**

No sensitivity analyses were performed.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.
Cost results
In the TCO analysis, the mean cost of antibiotics was $358 (median $31; range: 31 to 12,714) in the intervention group and $454 (median $9; range: 9 to 21,316) in the control group. The difference of $96 (-21.2%; 49.7, EUR 73.2) was statistically significant, (p<0.001). The mean hospital costs were $14,800 (median $8,000; range: 5,700 to 126,800) in the intervention group and $18,600 (median $10,000; range: 5,700 to 97,300) in the control group. The difference of $3,800 (-20.6%; 1,967.26, EUR 2,896.9) was statistically significant, (p=0.04).

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant as a cost-consequences analysis was performed.

Authors' conclusions
Compared with conventional prophylaxis, the longer and broader-spectrum antibiotic prophylaxis significantly decreased the incidence of sternal wound infection (SWI) and led to cost-savings in high-risk patients undergoing elective coronary artery bypass grafting (CABG).

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear in that the new proposed prophylaxis regimen was compared with the conventional one. The dosages and patterns of antibiotic administration were described clearly. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical data were derived from an RCT, which was appropriate for the study question. Usually, RCTs represent a robust source of data for the analysis of clinical end points. The major strengths of the analysis were numerous. Specifically, the use of power calculations in the planning phase of the study to ensure the enrolment of an adequate number of patients; the baseline comparability of the study groups; the extensive description of the sample selection process; the use of both ITT and TCO to analyse differences between the groups; the random allocation of patients to the treatment groups to reduce the impact of selection bias; the clear description of demographic and clinical characteristics of patients involved; the use of regression analysis to take the potential impact of confounding factors (e.g. differences in surgeons performing the interventions) into account; and the blinded nature of the study, which limited the impact of assessment bias. These aspects of the analysis enhance the robustness of the study.

The authors acknowledged that total masking was not feasible for technical reasons. A potential drawback of the study was the fact that the evidence came from a single institution, which might not be representative of other medical centres. Further, the authors stated that the study took place after the implementation of some changes in institutional and clinical patterns of care in their institution that were intended to deal with a perceived high incidence of SWI.

Validity of estimate of measure of benefit
No summary benefit measure was used since a cost-consequences analysis was carried out.

Validity of estimate of costs
The cost analysis was restricted to the costs of antibiotics and other hospital services. A breakdown of the cost items was not given and unit costs were not presented, except for the acquisition costs of the antibiotics. This might limit the possibility of replicating the analysis in other settings. The costs were derived from the hospital in a blinded fashion. The costs were highly skewed and typical statistical analyses of them were carried out. However, the impact of variations in costs or patterns of resource consumption was not investigated. The period during which the resource use data were gathered was reported, but the price year was not given. The authors stated that the inclusion of other costs such as extended hospital stay, readmission or stay in the intensive therapy unit would have further favoured the new antibiotic regimen.

Other issues
The authors stated that the primary clinical end point (incidence of SWI) was similar to estimates found in previous
studies. The issue of the generalisability of the study results to other settings was not addressed. Further, sensitivity analyses were not performed, which reduces the external validity of the analysis. The study referred to a sample of high-risk patients and this was strongly reflected in the authors’ conclusions, which emphasised that other agents may be necessary in other high-risk groups such as chronic lung disease or immunosuppression.

Implications of the study
The study results support the use of broad spectrum and prolonged (48-hour) antibiotic prophylaxis in patients undergoing elective cardiac surgery. The authors stressed the need to stratify patients before comparison, using an appropriate risk stratification system.

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MeSH
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