Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized 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 assessed the treatment of severe secondary peritonitis following an initial emergency laparotomy with planned relaparotomy compared with on-demand relaparotomy. Planned relaparotomies were performed every 36 to 48 hours after index laparotomy. The sequence of planned relaparotomies was terminated when a negative result of infection was found. On-demand relaparotomy was only performed in patients with clinical deterioration or lack of clinical improvement with a likely intra-abdominal cause. Clinical deterioration after the previous operation was considered if there were an increase of more than 4 points in the Multiple Organ Dysfunction Score or pre-specified surgical emergencies. Lack of improvement was considered if the Multiple Organ Dysfunction Score was unchanged for at least 48 hours following the index laparotomy or the previous relaparotomy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with severe secondary peritonitis, an APACHE-II score greater than 10, and who required an emergency laparotomy. The exclusion criteria were:

aged younger than 18 or older than 80 years;

peritonitis due to bowel perforation after endoscopy operated within 24 hours after perforation;

abdominal infection due to continuous ambulatory peritoneal dialysis catheter;

peritonitis caused by pancreatitis;

expected survival of less than 6 months due to malignancy;

severe brain damage due to trauma or anoxia; and

imperative relaparotomy.

Setting
The setting was inpatient care at a secondary care level. The economic study was carried out in the Netherlands.

Dates to which data relate
It was reported that patients were assessed for eligibility between November 2001 and February 2005. However, the
specific dates during which the effectiveness and resource data were collected were not reported. The price year was not reported.

**Link between effectiveness and cost data**
The costing was undertaken prospectively on the same patient sample that provided the effectiveness data.

**Study sample**
The authors reported that their study had 80% power to detect a difference in the primary combined outcome, with the on-demand strategy revealing a superiority of 10% absolute reduction in mortality and 10% absolute reduction of morbidity in survivors. A sample size of 111 in each group would have such a power. From 510 patients assessed for eligibility, 278 (54%) were excluded. Within the group of excluded patients, 228 (44.7%) met exclusion criteria, 43 (8.4%) refused informed consent and 7 (1.4%) were excluded by the surgeon. In total, 232 patients were randomised, 116 to each group. Four patients in the on-demand group and 7 in the planned strategy group did not receive the treatment to which they were randomised. One patient in the on-demand group was excluded after randomisation.

**Study design**
The study was a multi-centre, randomised, controlled trial that was carried out in 2 academic and 5 regional teaching hospitals in the Netherlands. Randomisation was performed centrally using a specialised computer-generated block sequence and stratified per study site according to the APACHE-II score as a minimisation factor (11 - 20 versus >20). Allocation was concealed until the interventions were assigned. Blinding of the patients and clinicians was not possible given the nature of the intervention. However, the operating surgeon was unaware of the allocated treatment strategy while performing the initial emergency laparotomy. Further, blinded investigators not involved with patient care collected and evaluated all data on the initial admission period and follow-up. Patients were assessed for eligibility between November 2001 and February 2005, and randomised patients were followed up for 12 months. In both groups, 1 patient withdrew consent and 2 were lost to follow-up (a total of 1.7% from the 232 randomised patients). The primary analysis included 112 patients in the on-demand relaparotomy group and 113 patients in the planned relaparotomy group.

**Analysis of effectiveness**
The primary outcome variable was a combination of all-cause mortality and major disease-related morbidity in surviving patients within the 12-month follow-up after index laparotomy. The authors specified major disease-related morbidity and counted it as an end point if it led to a surgical reintervention during the index admission or readmission during the 12-month follow-up (with or without the need for surgical intervention). Other clinical outcomes related to mortality and major morbidity were cumulative mortality during the 12-month follow-up, early mortality (first 60 days after the initial emergency operation), and major morbidity in survivors. The authors stated that the analysis was conducted on an intention to treat basis, although those lost to follow-up were excluded from the analysis. The study groups were comparable in relation to all patient and index laparotomy characteristics. The authors also performed a sub-group analysis for the APACHE-II score at the time of the index operation and by the hospital included, to determine whether treatment effects differed significantly between these groups.

**Effectiveness results**
It was reported that the combined primary end point occurred in 57% (n=64) of the patients in the on-demand group and 65% (n=73) of the planned group.

The risk difference was 7.5% (95% confidence interval, CI: -5 to 20; p=0.25) and the number-needed-to-treat was 13.

Cumulative mortality had a risk difference of 7.7% (95% CI: -7.5 to 16; p=0.23) and there was no difference in early mortality between the two groups (p=0.55 for 60 days).

The two groups had a morbidity risk difference of 4.4% (95% CI: -11 to 20; p=0.58).
Treatment effects with respect to the primary end point were comparable across APACHE-II score sub-groups and the 9 included hospitals (all tests for interaction were not significant as p>0.50).

**Clinical conclusions**

It was found that, compared with planned relaparotomy, the on-demand strategy did not result in statistically significant reductions in the primary outcomes of death or major peritonitis-related morbidity.

**Modelling**

Survival was calculated and compared using the Kaplan-Meier method and tested for differences using the log-rank test. The authors performed a sub-group analysis for the APACHE-II score at the time of the index operation and per including hospital. Logistic regression models were used for this purpose.

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

The authors did not derive a summary measure of benefit. In effect, a cost-consequences analysis was performed. See the 'Analysis of Effectiveness' section for the clinical outcomes measured. The benefits were not discounted as the duration of follow-up was 12 months.

**Direct costs**

The authors estimated the costs from the perspective of the health care system. Direct medical costs were estimated using primary data on resource use. Resource use was presented for both groups for the following categories: relaparotomies, percutaneous interventions, diagnostic computed tomography (CT) scans, length of hospital stay, intensive care unit stay with and without mechanical ventilation, and days in hospital due to readmissions. The authors also identified further categories (administration of antibiotics, elective reoperations, length of stay in rehabilitation centres, health care provided by district nurses, and enterostomy care during 12-month follow-up), although these were not presented. It was reported that the costs per patient were calculated by multiplying volumes of resource with unit costs. The authors reported using Dutch guidelines for some of the unit costs while others were determined at the Academic Medical Center, Amsterdam. None of the aforementioned unit costs were presented. The authors reported the mean direct medical costs per patient after 12 months for both groups. The price year was not reported. Discounting was not necessary as the time horizon for the cost estimation was 1 year.

**Statistical analysis of costs**

The significance of differences in health care utilisation was tested using the chi-squared test or Mann-Whitney U-test (at a 5% significance level), where appropriate. The differences analysed and reported were in the total number of relaparotomies, the proportion of patients with at least three relaparotomies, the number of negative findings for the first relaparotomy, the proportion of patients with positive findings at relaparotomy, the number of CT scans, and the number of CT- or ultra-sound-assisted percutaneous drainage. CIs for differences in the mean costs were reported. These were based on log-transformed cost data.

**Indirect Costs**

Productivity costs were not considered.

**Currency**

Euros (EUR) and US dollars ($).

**Sensitivity analysis**

There was no other examination of uncertainty for the economic analysis.
Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean direct medical costs per patient after 12 months of follow-up, including the index admission period, were 23% lower in the on-demand group. These costs were EUR 62,741 ($86,077) for the on-demand strategy and EUR 81,532 ($111,858) for the planned strategy. There was an absolute difference of EUR 18,791 per patient (95% CI: 6,819 to 31,166), ($25,780 per patient, 95% CI: 9,355 to 42,758).

With respect to health care utilisation results it was reported that the proportion of patients with at least 3 relaparotomies was 9% in the on-demand group compared with 24% in the planned group, (p<0.001).

Negative findings for the first relaparotomy were seen in 31% of the on-demand group and in 66% of the planned group, (p<0.001).

The proportion of positive findings at relaparotomy was comparable in both strategies, (p=0.6).

The number of CT scans was comparable between the two strategies but not CT- or ultrasound-assisted percutaneous drainage (less frequent in the on-demand group).

Synthesis of costs and benefits
There was no synthesis of the costs and benefits as this was a cost-consequences study.

Authors' conclusions
Patients in the on-demand relaparotomy group did not have a significantly lower rate of adverse outcomes compared with patients in the planned relaparotomy group. However, they did have a substantial reduction in relaparotomies, health care utilisation and medical costs. Overall, "on-demand relaparotomy may therefore be considered the preferred surgical strategy in patients with severe peritonitis".

CRD COMMENTARY - Selection of comparators
A justification was provided for the technologies compared. Both interventions were widely used relaparotomy strategies despite the growing support for the on-demand strategy. The preferred strategy for mild peritonitis was on-demand relaparotomy, but there was no evidence from a randomised trial to draw the same opinion with respect to severe peritonitis. You should decide if these represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised controlled trial. The study sample was representative of the study population. In addition, the patient groups were shown to have been comparable at analysis. The method of randomisation, blinding, length of study and loss to follow-up were all reported, suggesting that the internal validity of the study is likely to be good. Appropriate statistical analyses were undertaken to take potential biases (intention to treat, CIs and p-values reported) and confounding factors (sub-group analysis for APACHE-II score and hospital) into account. Power calculations were reported to ensure that the size of the study sample was adequate.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of benefit. In effect, a cost-consequences analysis was performed.

Validity of estimate of costs
The authors did not explicitly state the perspective of their study, but it appears to have been that of the health care
system. All the relevant categories of costs and costs within each category appear to have been included in the analysis. The resource quantities were collected alongside the trial, and most of those identified by the authors were presented with a stochastic analysis of the difference between strategies. The sources of the unit costs were presented, but not the unit costs themselves. The authors only reported the average medical costs. Discounting was not necessary given that the time horizon for the cost estimation was 1 year. Uncertainty in the cost data was evaluated for differences in resources used and direct costs. The cost data were not reported adequately as there was no reference to the price year or resource dates, the unit costs were not presented, and currency conversion (EUR to $) was not clarified. There was no sensitivity analysis to address variation in the unit costs or service provision for different settings. The fact that the cost data were poorly reported may have implications for the generalisability of the study beyond the study setting.

Other issues
The authors compared their findings with those from other studies and generally found them to be in agreement. The issue of generalisability to other settings was discussed. Variations in several factors relating to the patient population were acknowledged, but the impact of these on the results of the economic analysis was not studied. The authors do not appear to have presented their results selectively and they appear to have provided a balanced discussion. The study considered patients with secondary peritonitis and this was reflected in the authors' conclusions. Some limitations were pointed out. For example, considerations for relaparotomy concerning clinical, laboratory and imaging parameters was not explicit given that the final decision to perform a reoperation in the on-demand setting was made within a multidisciplinary team.

Implications of the study
Despite not resulting in statistically significant reductions in the primary outcomes, the on-demand strategy resulted in significant reductions in health care utilisation and costs, suggesting that it might be the preferred strategy. The authors recommended that future research focus on optimising adequate and timely selection of patients for relaparotomy by the identification of predictive variables.

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