

CAGS AND ACS EVIDENCE-BASED REVIEWS IN SURGERY. 28

Comparison of on-demand and planned relaparotomy for secondary peritonitis

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The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”¹ The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence-Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) and is supported by an educational grant from ETHICON and ETHICON ENDO-SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson and ETHICON Inc. and ETHICON ENDO-SURGERY Inc., divisions of Johnson & Johnson Inc. The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

SELECTED ARTICLE

van Ruler O, Mahler CW, Boer KR, et al. Comparison of on-demand vs. planned relaparotomy strategy in patients with severe peritonitis. A randomized trial. *JAMA* 2007; 298:865–73.

ABSTRACT

Objective: To compare patient outcomes, healthcare utilization and costs of on-demand and planned relaparotomy in patients with severe secondary peritonitis. **Design:** Randomized, nonblinded controlled trial. **Setting:** Two academic and 5 regional teaching hospitals in The Netherlands. **Patients:** A total of 232 patients with a diagnosis of peritonitis, confirmed during an index laparotomy, and an acute physiology and chronic health evaluation (APACHE II) score of greater than 11. **Intervention:** The planned relaparotomy ($n = 116$) was performed every 36–48 hours after the index laparotomy to inspect, drain, lavage and perform other necessary abdominal interventions for residual peritonitis or new infections. The sequence of planned relaparotomy was terminated when negative findings were found macroscopically. On-demand relaparotomy ($n = 116$) was only performed in patients with clinical deterioration or lack of improvement with a likely intra-abdominal cause. Deterioration was considered if there was an increase of more than 4 points in the multiple organ dysfunction score or a prespecified surgical emergency (e.g., abdominal compartment syndrome, intra-abdominal bleeding with decrease in hemoglobin despite replacement and hemodynamic instability, burst abdomen, perforation of visceral organ, anastomotic leak, intra-abdominal abscess that cannot be drained percutaneously, ischemia/necrosis of a visceral organ). **Primary outcome:** A combination of all-cause mortality and major disease-related morbidity in surviving patients within the 12 month follow-up period after the index laparotomy. Secondary outcomes included health care utilization and direct medical costs during the follow-up period. **Results:** Comparing on-demand with planned relaparotomy, there was no significant difference in the primary outcome (57% v. 65%, $p = 0.25$), in mortality alone (29% v. 36%, $p = 0.22$), or in morbidity alone (40% v. 44%, $p = 0.58$). A total of 42% of patients in the on-demand group had a relaparotomy compared with 94% of patients in the planned relaparotomy group. Thirty-one percent of first relaparotomies were negative in the on-demand group compared with 66% in the planned relaparotomy group ($p < 0.001$). Patients in the on-demand group had shorter stays in the intensive care unit than those in the planned relaparotomy group (median 7 v. 11 d, $p = 0.001$) in addition to shorter stays in hospital (median 27 v. 35 d, $p = 0.008$). The medical costs for patients in the on-demand group were 23% lower than those for patients in the planned relaparotomy group. **Conclusion:** Patients in the on-

demand group did not have significantly lower mortality or major peritonitis-related morbidity than those in the planned relaparotomy group, but did have fewer relaparotomies and a substantial reduction in health care utilization and medical costs.

COMMENTARY

This multicentre randomized trial focused on patients with secondary peritonitis due to conditions such as gastrointestinal perforation, mesenteric ischemia and anastomotic leakage, with systemic manifestations of sepsis (APACHE score ≥ 11). Of note, patients with pancreatitis and patients requiring damage-control procedures with imperative re-explorations were excluded from the study. Patients were randomly assigned to the on-demand or planned relaparotomy groups at a central site using a computer-generated block sequence after the clinical diagnosis of peritonitis was confirmed during the initial laparotomy. Random assignment was stratified based on APACHE score (11–20 v. > 20), and the operating surgeon was not informed of group assignment until the initial laparotomy was completed. Informed consent was obtained preoperatively, but random assignment took place after the clinical diagnosis of peritonitis was confirmed at the index laparotomy.

A total of 510 patients were screened for enrolment: 228 were excluded, including 131 with APACHE scores less than 11, 39 who were younger than 18 or older than 80 years, and 58 who met other exclusion criteria. It is unclear whether the latter were excluded owing to imperative relaparotomy (e.g., abdominal packs left in, stapled bowel ends left in). If so, the results of this study do not apply to the sickest 10% of patients. Arguably, these patients required repeat surgery to remove packs or for reanastomosis and, therefore, cannot be included among patients undergoing planned relaparotomy solely for peritonitis. Forty-three patients refused consent, and 7 were excluded by the primary surgeon.

A total of 116 patients were randomly assigned to on-demand relaparotomy. One patient was excluded because of an intraoperative diagnosis of pancreatitis, 2 inadvertently underwent planned relaparotomy and the surgeon deliberately changed to a planned relaparotomy approach in 2 patients. One patient withdrew from the study, and 2 were lost to follow-up, leaving 112 patients in the primary analysis. A total of 116 patients were randomly assigned to planned relaparotomy. Seven patients did not receive their first planned relaparotomy: 2 who died the day of the index laparotomy, 1 who was too ill for laparotomy, 2 in whom the surgeon decided not to operate, and 2 patients who declined relaparotomy. One patient withdrew from the study, and 2 were lost to follow-up, leaving 113 in the primary analysis.

The study was designed to detect superiority of the on-demand strategy, with a 10% absolute reduction of mortality and a 10% absolute reduction in morbidity. This

translates into a reduction of the primary outcome from 44% to 28%. A sample size of 111 in each group has a power of 80% to detect such a difference, with a 1-sided α of 0.05. A 5% dropout rate was expected and accounted for.

Based on a literature review, these estimates are accurate, although the reduction in mortality and morbidity could be considered somewhat aggressive. In addition, the least conservative statistical analysis was chosen, using a 1-sided rather than a 2-sided value for α . The authors likely chose to base the sample size estimate on a 1-sided test to decrease the number of patients required. It is reasonable to do so when the treatment can only do "some good" and no harm. That is questionable in this scenario, where both treatment scenarios could definitely be more harmful (e.g., more anesthetics, increased risk of small bowel injury in the planned relaparotomy v. untreated unsuspected septic process in the on-demand group).

The sample included a reasonably homogeneous group of well-matched and "sick" patients: median age 69 years, median APACHE score of 15, a 60% incidence of major comorbidity, a 90% or greater incidence of positive intra-peritoneal cultures intraoperatively and a 12-month mortality of about 30%. Thus, the study is believable and involves the type of patients in whom the question of planned relaparotomy versus on-demand relaparotomy is debated. Interestingly, 66% of the planned relaparotomies were "negative laparotomies" and thus nontherapeutic, a finding that is not encouraging in support of a strategy of planned relaparotomy. Only 30% of the on-demand laparotomies were "negative laparotomies," representing a false-positive diagnosis or suspicion of sepsis.

The investigators found no significant difference between the groups in the composite primary outcome, or in major morbidity or mortality taken separately. A total of 57% of patients in the on-demand group versus 65% in the planned relaparotomy group reached a primary outcome. The absolute difference was 7.5% (95% confidence interval [CI] -5% to 20%, $p = 0.25$). The wide 95% CI suggests that the on-demand strategy may result in a 5% worse outcome or a 20% better outcome. Thus, one cannot state with any confidence that the 2 treatment strategies are equivalent and that the risk of a type II error is quite high (i.e. concluding that there is no difference when in truth there is one). The relative risk of death or major morbidity within the 12-month follow-up period for the on-demand group was 0.88 (95% CI 0.72-1.10, $p = 0.25$).

There were significant reductions in the duration of mechanical ventilation, length of stay in the intensive care unit, length of stay in hospital, health care utilization and direct medical costs in the on-demand group compared with the planned relaparotomy group. These differences persisted even after accounting for severity of illness. Although the authors speculated that multiple surgical lavages in the planned relaparotomy group may have lengthened recovery time by amplifying the systemic

inflammatory response, the observed differences in health care utilization may simply reflect the more intensive and repetitive nature of the planned relaparotomy strategy, which often requires patients to remain on mechanical ventilation between procedures. It was interesting, however, that the planned relaparotomy group required a significantly higher number of percutaneous drainage procedures, a phenomenon that would seem to defeat the purpose of serial abdominal washouts. In these secondary outcomes, it is particularly important that interventions within the first year after initial laparotomy were considered, as many of these patients continue to have problems requiring intervention and readmission to hospital long after the traditional 30-day window in which postoperative morbidity and mortality are recorded. Incisional hernia, very common among these patients, was considered and was similar in both groups. Not considered was the need for advanced wound care, including the use of vacuum-assisted closure. This is likely a minor consideration, although the costs of these complex wound-management strategies can be considerable.

Although the benefits of on-demand relaparotomy were seen even in patients with higher APACHE scores in pre-defined analyses, the results of the study may not be generalizable to the sickest patients — those with so much contamination, necrosis, edema or physiologic instability that abbreviation of the index operation, repeat laparotomy and delayed closure are deemed imperative by the surgical team. These patients, who might arguably be the greatest beneficiaries of a planned relaparotomy approach, were excluded from the study. Despite the decisive results in favour of on-demand relaparotomy, there still appears to be a role, and even a necessity, for planned relaparotomy as an exit strategy in selected unstable patients.

The results of the study support those of a previous meta-analysis, favouring on-demand rather than planned relaparotomy.¹ The meta-analysis contained data from observational studies only; therefore, the data from this prospective trial were both needed and important. However, the authors are careful to point out that decreased reliance on the planned relaparotomy strategy will require surgeons to be even more vigilant in suspecting complications after the initial procedure. Although the monitoring protocol in the on-demand group was not specific (it led to a nontherapeutic relaparotomy rate of 31%), it did draw attention to the possibility that complications after the index laparotomy may be detected early through rigorous surveillance algorithms, including the use of computed tomography.

Competing interests: None declared.

Reference

1. Lamme B, Boermeester MA, Reitsma JB, et al. Meta-analysis of relaparotomy for secondary peritonitis. *Br J Surg* 2002;89:1516-24.