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Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones

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CAGS Evidence Based Reviews in Surgery

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Selected article

Boerma D, Bauws EJ, Keulemans YA, Janssen IM, Bolwerk CJ, Timmer R, et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. *Lancet* 2002;360:761-5.

Abstract

Question: Is a wait-and-see policy better than a cholecystectomy within 6 weeks after endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy and clearance of the common bile duct of stones? **Design:** Randomized controlled trial. **Setting:** A multicentre trial that included 1 academic centre and 8 community hospitals in The Netherlands. **Patients:** One hundred and twenty patients with proven gallbladder stones who underwent endoscopic sphincterotomy and stone extraction. **Intervention:** Patients were randomly allocated using a computer generated randomization scheme by an independent trial bureau to either a wait-and-see approach (n = 64) or laparoscopic cholecystecomy (n = 56). **Outcome measure:** At least 1 biliary event during a 2-year follow-up. **Results:** Twelve patients were lost to follow-up immediately. Of the 59 patients randomized to a wait-and-see approach (and available for analysis), 27 (46%) had recurrent biliary symptoms versus 1 (2%) of 49 patients after laparoscopic cholecystectomy (LC) (risk ratio = 22.42, 95% confidence interval [CI] 3.16–159.14, $p < 0.001$). Twenty-two (81%) of the 27 wait-and-see patients underwent cholecystectomy, mainly for biliary pain (13 patients) or acute cholecystitis (7 patients). The rate of conversion to open cholecystectomy was 55% in patients allocated to the wait-and-see group compared with 23% for those who underwent immediate LC (p = 0.010). **Conclusion:** A wait-and-see policy after endoscopic sphincterotomy should not be recommended as

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the standard treatment since 46% had at least 1 more biliary event and 37% required cholecystectomy.

Commentary

Overall, 10% of patients with gallstones may be found to have concomitant common-bile-duct (CBD) stones.[1] Arguably, most CBD stones will remain asymptomatic, but some patients will suffer significant complications such as jaundice, cholangitis and acute pancreatitis. In the nonurgent context, it is not clear whether these conditions are best treated by a fully operative (laparoscopic) approach or by a staged approach with the use of ERCP.[2,3] The present study does not address this contentious issue but rather aims to determine the answer to the following question: When a patient who is fit to undergo LC has had an ERCP with complete stone clearance from the CBD, which of the following 2 clinical approaches is best: an "immediate" cholecystectomy within 6 weeks of the ERCP–sphincterotomy, or a wait-and-see approach whereby the patient only undergoes LC, should the need arise.

To best answer the question, the authors performed a randomized controlled trial (RCT) in which patients were allocated to each group within 6 weeks of ERCP-duct clearance. Provided the study is done well, an RCT provides the best evidence to answer a clinical question regarding treatment effectiveness. According to the Cochrane Collaboration, the 3 most important attributes of an RCT to ensure that bias is minimized are that the randomization scheme is concealed, there is blinding of outcome and follow-up is complete.[4] If so, the study should have internal validity.

On the other hand, it is also important to know what proportion of eligible patients were actually included in the trial. If only a very small proportion of potential patients were recruited, one might worry about how representative this sample is, thus compromising the *external validity* ("generalizability") of the trial. Generalizability could also be compromised if the accrued sample of patients were in some way not representative of our own patients or had in fact been selected on the basis of a specific trait. In this trial, all consecutive eligible patients were considered for inclusion and in one hospital the characteristics of subjects in the trial were compared with the characteristics of patients involved in another local study on "policy after sphincterotomy." Although a crafty effort, a formal record of all potential patients, specifying the proportion ultimately recruited would have been more convincing.

In this study, randomization was performed by an independent agent, thus minimizing the risk of overt or inadvertent tampering with the randomization scheme. Despite randomization, the 2 groups have some differences in baseline characteristics. Unfortunately, randomization may not control for imbalances in every possible baseline variable; in fact, some are bound to occur just by chance. Stratification is an important tool in the randomization process designed to control for variables that are known pre hoc to be important. In this study, subjects were stratified by age and centre before randomization, so the groups are similar with respect to age. However, 6% of the LC group and 17% of the wait-and-see patients presented with cholangitis or pancreatitis. As well, 52% of the wait-and-see patients had a patent cystic duct, compared with 68% in the LC group, meaning that the wait-and-see group were at higher risk for recurrent symptoms. To evaluate the possible impact of these differences, the authors performed a univariate post-hoc analysis. Although the rates of pancreatitis, cholangitis and cystic duct patency did not achieve statistical significance, "younger age" (54 yr v. 63 yr) was found to be related to a greater risk of recurrent symptoms. This observation may explain the discrepancy between the rate of recurrent symptoms in this trial and those from previous nonrandomized studies, which dealt primarily with an older population. The quantitative effects of these imbalances, however, cannot be assessed because the authors elected not to perform a multivariate analysis because of the relatively small sample size and the unfavourable ratio of outcome events to variables. It is therefore not possible to tell if these baseline imbalances could have accounted for the observed difference in recurrent biliary symptoms.

Blinding, by necessity, was incomplete in this trial. As in many trials comparing a medical (wait-and-see) to a surgical approach (cholecystectomy within 6 wk), blinding of *the patient* or *the clinician in charge of the patient* was simply not feasible. However, *the individual recording the outcome data* was blinded, and interviewers recorded data objectively according to predefined outcome criteria through standardized interviews. The authors are therefore able to convince us of a dissociation between the physicians treating the patients (and referring them for cholecystectomy on demand) and the determination of the study outcomes.

The authors do include a CONSORT (Consolidated Standards of Reporting Trials) diagram[5] to track the outcome of all randomized patients, so we can determine the outcome of the randomized subjects in the trial. This is particularly important in this trial because of the potential for dropouts, given that a significant delay might have occurred between randomization and the scheduled cholecystectomy (up to 6 wk later). Analysis was ultimately performed on 49 (88%) of 56 randomized patients in the LC group and 59 (92%) of 64 in the wait-and-see group. Altogether, 8% of patients crossed over from one group to the other. This does not compromise the validity of the results because a generally accept-

able upper limit is around 10%. Ultimately, 46% patients in the wait-and-see group suffered recurrent biliary symptoms compared with 2% in the immediate LC group. Recurrent symptoms in the wait-and-see group were related to the remaining gallbladder because cholecystectomy relieved these symptoms in every case. Moreover, in those patients who had symptoms, nearly two-thirds had recurrent biliary colic, and a little over one-quarter had acute cholecystitis. No episode of pancreatitis or cholangitis was recorded. It is also clinically significant that over half (12 of 22) of the wait-and-see patients who underwent LC required conversion to an open procedure and that a substantial proportion of these suffered complications. However, a high rate of conversion present in the immediate LC group (20%) suggests that there may be a low trigger for conversion in the participating Dutch hospitals.

What this study adds to the literature has been a subject of debate among the authors of this review. As after any RCT, the results must be interpreted in relation to existing nonrandomized literature. RCTs are usually performed in ideal patients under ideal conditions. Furthermore, they may include small numbers of patients followed up for a relatively short time and therefore, as stated previously, may lack generalizability. Evidence-based medicine has been defined as "integrating individual clinical expertise with the best available clinical evidence from systematic research."[6] Thus, evidence from RCTs must be taken in the context of several other sources of evidence including nonrandomized studies and expert clinical opinion, and, fulfilling the ethical principle of autonomy, the physician must also integrate the evidence from these various sources with his or her own clinical experience in order to disclose information to patients, provide advice and make recommendations.[7]

With respect to the rate of symptom recurrence in the wait-and-see group, the 95% CI on the reported 46% point estimate can be calculated and ranges from 32.7% to 59.2%. This means that the lowest estimate of this value is still 3 times greater than the average estimate from previous nonrandomized trials (around 10%). Expressed as a risk ratio (how many times recurrent symptoms are more likely to occur in the wait-and-see group), the 95% CI of the difference between both groups is 3.16–159.14. These numbers may appear compelling, but what does "3.16 times greater chances of biliary symptoms developing" mean to a patient?

If patients choose to wait and see, they would have an approximately 50% chance of having recurrent symptoms and a 40% chance of requiring a cholecystectomy. From the perspective of a patient who may be averse to surgery, that also means that a wait-and-see approach would lead to a slightly better than 50% chance of *no* recurrent symptoms and a 60% chance of *avoiding* a cholecystectomy at 2.5 years. Should he or she require LC, the chance of conversion to an open procedure (55% v. 23%) and the risk of postoperative complications (32% v. 14%) would be great. Interpretation of the trade-offs highlighted by this RCT may thus allow a patient to decide which strategy he or she prefers based on his or her values. Nevertheless, the conclusion for most surgeons is that immediate LC is the preferred option and should be recommended. Existing literature clearly shows that elective LC can be performed very safely in patients who are operative candidates. Moreover, there is a real limitation in the significance of this study owing to the small number of patients and the relatively short trial duration (median 30 mo). Both of these are common limitations in surgical RCTs. Cholelithiasis is a lifelong disease, and most patients who are surgically fit probably have 20–30 years of expected life. A greater rate of recurrent symptoms could therefore have been reasonably expected with a follow-up of 10 years or more. Also, the study is not powered to address the development of rare but life-threatening complications of biliary tract disease such as biliary pancreatitis.

A conclusion based on the limitations of this study might therefore be the singular recommendation of the need for confirmatory data on the risks of a wait-and-see policy, not from a level 1 RCT but rather through long-term patient follow-up of a large cohort of patients in validated credible registries or databases.

Competing interests: None declared.

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