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Trial sequential analyses of meta-analyses of complications in laparoscopic vs. small-incision cholecystectomy: more randomized patients are needed

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Abstract

Objective: Conclusions based on meta-analyses of randomized trials carry a status of "truth." Methodological components may identify trials with systematic errors ("bias"). Trial sequential analysis (TSA) evaluates random errors in meta-analysis. We analyzed meta-analyses on laparoscopic vs. small-incision cholecystectomy regarding different outcome measures for the occurrence of type I errors.

Study Design and Setting: Using TSA, we calculated the required information size (IS) and the trial sequential monitoring boundaries regarding complications in our Cochrane review with meta-analyses of cholecystectomy. For each outcome, we calculated a low risk of bias heterogeneity-adjusted IS. As a sensitivity analysis, we calculated an a priori heterogeneity-adjusted IS.

Results: According to the trial sequential analyses based on a low risk of bias heterogeneity-adjusted IS definitive evidence may be reached by conducting one more randomized trial. Information may be required on 582 and 119 additional randomized patients to evaluate the effect on severe complications and serious adverse events (SAEs), respectively.

Conclusion: Our results provide incentives to conduct a new trial with a low risk of bias focusing on a new composite outcome measure of SAEs to obtain conclusive evidence on which operative method to recommend.

Keywords: Cumulative meta-analysis; Trial sequential analysis; Meta-analysis; Random error; Cholecystectomy; Trial sequential monitoring boundaries

1. Introduction

The number of Cochrane reviews and the availability of The Cochrane Library worldwide have increased during the last decade [1]. The development and application of evidence-based guidelines, usually based on the highest level of evidence, that is, systematic reviews of randomized trials with low risk of bias, have also increased [2].

The conclusions based on such reviews with meta-analyses may carry a status of "truth," and skepticism tends to be sparse. However, there is a high probability that differences between treatments are found because of random errors ("the play of chance") [3,4], systematic errors ("bias") [5–8], and design errors ("wrong design to answer the question posed" or "wrong context," e.g., lack of sufficient education in one of the interventions) [9]. Potentially spurious results may arise because of random errors (type I and II errors), when a limited number of trials and patients are included and with frequent updating of the cumulative meta-analysis [3,4].

In the planning of a randomized trial, the sample-size calculation provides an insight into the ability to detect an intervention effect with sufficient power. The sample size is calculated to detect a prespecified intervention effect with a risk of type I (α) and type II (β) error [10]. It is

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What is new?

- More randomized patients are needed before conclusive evidence can direct which technique of cholecystectomy should be preferred.
- Our results strongly suggest that a new cholecystectomy trial with low risk of bias should be conducted focusing on a composite outcome measure of SAEs rather than focusing on a single rare outcome.
- TSA should be considered for incorporation in cumulative meta-analyses to assess the risk of random error.

inappropriate to make conclusions based on small differences between treatments from a randomized trial with only few patients included. Likewise, it may be inappropriate to draw conclusions from a meta-analysis when information is sparse [4]. Without evaluating how much information is needed and how much we have at hand, we may not be able to reliably assess the results. Consequently, we might well draw inappropriate conclusions because of random errors in a cumulative meta-analysis with too little information.

We have conducted trial sequential analysis (TSA), based on the calculation of the heterogeneity-adjusted required information size (IS) and the analysis of the cumulative *z*-curve [4,11–15]. In a cumulative meta-analysis, the pooled intervention effect estimate is updated whenever a new trial is added according to the chronological sequence of publishing. The cumulated *z*-values can be calculated and plotted against the new cumulated IS obtained [4,11–15]. Further, trial sequential monitoring boundaries (TSMBs) can be constructed and the relation of the *z*-curves to the boundaries may determine whether firm evidence is established or not in the meta-analysis [4,11–15].

We conducted a Cochrane Hepato-Biliary Group review with meta-analyses comparing laparoscopic vs. small-incision cholecystectomy for patients with symptomatic cholecystolithiasis [16]. This review is in the process of being updated, and 15 trials with a total of 2,582 randomized patients were included [17]. The question is whether the required IS has been reached to detect or reject a worthwhile and realistic intervention effect or whether possible differences reflect spurious $P < 0.05$ values (type I error).

1.1. Aim

The aim of this study was to calculate the required IS and the TSMB for the meta-analyses of our Cochrane review on laparoscopic and small-incision cholecystectomy for patients with symptomatic cholecystolithiasis.

2. Methods

2.1. Data

There are many kinds of complications in cholecystectomy; they were categorized into four subcategories in our Cochrane review [16]: intraoperative, minor, severe, and bile duct injury. Further, total complication proportions were calculated. Bile duct injuries were registered separately from the other complications and hence not counted as intraoperative, severe, or minor adverse event. Likewise, the intraoperative complications, excluding bile duct injuries, were categorized separately from the minor and the severe complications. As the number of complications was reported and not the number of patients with complications, patients may occasionally have been double counted [16].

Intraoperative, minor, severe, and bile duct injury complications have been considered to be independent outcome measures. The total complication category, however, summarizes all complications and is thus not independent of the other outcome categories. We considered total complications the most important outcome measure in our systematic review. However, total complications also include complications, which can hardly be considered critical for decision making according to the Grade categorization of outcomes [9,18–20]. Therefore, it seems more sensible to compile all serious adverse events, considered critical for decision making, into a single composite outcome measure called "serious adverse events" (SAE). SAE includes mortality, bile duct injuries, severe complications, and clinically important intraoperative complications.

From a statistical point of view, analyses of multiple outcome measures require *P*-value adjustment, which is difficult when outcomes are not strictly independent. So despite the fact that all the outcomes defined may be of interest, we chose to analyze only the most important ones to reduce inflation of type I error by multiplicity of testing. Therefore, we analyzed mortality, the four complication subcategories, and total complications. Additionally, a composite outcome measure of SAE was generated and evaluated post hoc as a hypothesis-generating analysis.

2.2. Zero-event trials

Several trials included in our review had zero events in one or both groups of surgical intervention. In a previous study, we evaluated the impact of different meta-analytical statistical methods on the conclusions of our review depending on the handling of the zero-event problem [21]. Based on this study and recommendations from the literature, we decided to use an empirical continuity correction of 0.01 in zero-event trials for the present analyses [16,21–24].

2.3. Bias protection

As randomized clinical trials with a high risk of bias may overestimate intervention effects [5,8,25], results of