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Interrupted time-series analysis yielded an effect estimate concordant with the cluster-randomized controlled trial result

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Abstract

Objective: We reanalyzed the data from a cluster-randomized controlled trial (C-RCT) of a quality improvement intervention for prescribing antihypertensive medication. Our objective was to estimate the effectiveness of the intervention using both interrupted time-series (ITS) and RCT methods, and to compare the findings.

Study Design and Setting: We first conducted an ITS analysis using data only from the intervention arm of the trial because our main objective was to compare the findings from an ITS analysis with the findings from the C-RCT. We used segmented regression methods to estimate changes in level or slope coincident with the intervention, controlling for baseline trend. We analyzed the C-RCT data using generalized estimating equations. Last, we estimated the intervention effect by including data from both study groups and by conducting a controlled ITS analysis of the difference between the slope and level changes in the intervention and control groups.

Results: The estimates of absolute change resulting from the intervention were ITS analysis, 11.5% (95% confidence interval [CI]: 9.5, 13.5); C-RCT, 9.0% (95% CI: 4.9, 13.1); and the controlled ITS analysis, 14.0% (95% CI: 8.6, 19.4).

Conclusion: ITS analysis can provide an effect estimate that is concordant with the results of a cluster-randomized trial. A broader range of comparisons from other RCTs would help to determine whether these are generalizable results.

Keywords: Interrupted time-series analysis; Randomized controlled trial; Health systems; Evaluation; Research methods; Comparative effectiveness

1. Introduction

Rigor and feasibility are often conflicting goals in the choice of study designs for evaluating health system interventions [1]. Randomized trials may be difficult to conduct for both practical and political reasons [2,3]. Simple but weak evaluation designs, such as comparing outcomes before and after an intervention, are often feasible but may yield misleading findings [4,5]. The high cost and slow pace of randomized, controlled trials (RCTs) can also impede their use in health systems research [6], although they sometimes may be quicker and less costly than observational studies [7]. Unfortunately, little is known about the relative validity of different approaches to evaluating the effectiveness of health system interventions, beyond theoretical arguments. The need for more empirical evidence on the validity of findings from randomized and nonrandomized study designs was recently emphasized by the Methodology Committee of the Patient-Centered Outcomes Research Institute [8].

In one such design, interrupted time-series (ITS) analysis, data collected at multiple time points before and after an intervention are evaluated to determine whether the intervention produced a discontinuity (change in level or slope) in comparison with the underlying secular trend [9]. This method is promoted as "a particularly strong quasi-experimental alternative to randomized designs when the latter are not feasible" [10, p. 172]. Frequently, the data used in ITS analyses of health system interventions are collected routinely as part of the delivery of care or the reimbursement process. Thus, this approach may be an attractive option that is both feasible and rigorous. However, to

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What is new?

- An interrupted time-series analysis yielded an effect estimate that is concordant with a conventional cluster, randomized, controlled trial analysis.
- This finding provides empirical support for the hypothesis that interrupted time-series analyses can provide reliable estimates of the effects of health system interventions.
- A broader range of comparisons would help to determine whether the findings from this study are generalizable.

our knowledge, no empirical studies have explored whether effect estimates from an RCT would be replicated by ITS analyses of the same data.

Between April 2002 and December 2003, we (A.F. and A.O.) conducted a cluster-randomized, controlled trial (C-RCT) with primary care physicians in Norway:—the Rational Prescribing in Primary Care (RaPP)—trial [11]. The trial was financed by the Norwegian Ministry of Health, motivated by the increased use of newer, expensive drugs for cardiovascular risk reduction, such as calcium channel blockers and angiotensin receptor blockers that are generally no more effective than older, less expensive medications.

We developed a multifaceted intervention, including educational outreach visits and computerized reminders, to encourage increased use of recommended antihypertensive medication (low-dose diuretics) [11]. A total of 146 primary care practices from two areas of Norway were recruited (participation rate, 38%), half of which were randomized to receive the intervention. We block randomized within two geographical areas to ensure balance in the number of practices in the intervention and control groups. The size of the blocks varied randomly between two, four, and six. The allocation list was generated by a colleague not directly involved in the research project with software from http://www.randomization.com. We gave our colleague identification numbers that represented each recruited practice, and she informed us whether the practice was allocated to the intervention or control group [11].

Practices in the intervention group were visited by a trained pharmacist who presented the physicians with recently published clinical guidelines that included a recommendation to use low-dose diuretics as first-line antihypertensive medication. We installed a software package during the visit that enabled extraction of data from the electronic medical record system and immediate feedback to the physicians regarding their current prescribing practices. The software also provided on-screen reminders about recommended first-line medication, which were triggered when patients returned after any recording of high blood pressure. Outcome data were collected from electronic medical records. The flow of participating practices is shown in Fig. 1.

The intervention proved successful. The trial showed that prescribing the recommended antihypertensive drugs doubled in the intervention group compared with the control practices [11]. The analysis followed the conventional approach of comparing outcomes in the two groups aggregated over the intervention period, while adjusting for differences between the groups during the preintervention period.

After the trial was completed, we questioned whether the results would have been similar if we had used ITS analysis instead of conducting an RCT. The prescription data we collected for this trial were dated, providing an opportunity to investigate this question by analyzing the data with both methods. The objective of study was to compare the effect estimates of these two approaches.

2. Methods

We reanalyzed the primary outcome from the trial with data most suitable for ITS analysis: prescribing low-dose diuretics. The data from the trial included all prescriptions for patients initiated on antihypertensive medication during the year before and the year after the launch of the intervention. To accommodate the ITS analysis, we decided to exclude a small number of prescriptions ($n = 178$) from more than 12 months before or more than 12 months after the intervention, which had been included in the original trial analysis. We did this before running the analyses.

The C-RCT effect estimate was recalculated by comparing the postintervention proportions of recommended prescribing in the intervention and control groups, using baseline prescribing levels for each practice as covariates (analysis of covariance) in a generalized estimating equation model incorporating all observations (prescriptions) while controlling for clustering effects—a recommended approach to analysis of cluster trials [12]. The reanalysis of the C-RCT was done to ensure that the same data were used for the C-RCT and the ITS analysis, and that the same metric was used for effect estimates (absolute risk differences).

Initially, we conducted the ITS analysis using data only from the intervention arm of the trial, because our main objective was to compare the findings from a single-group ITS analysis with the findings from the C-RCT. This addressed our original research question directly: What would the findings have been had we conducted a simple, uncontrolled ITS analysis rather than a C-RCT? All prescriptions were organized according to the number of days before or after the intervention took place, from which we constructed a time series of monthly rates of prescribing of