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Evaluating the Comparative Self-Controlled Cases Series Method

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Abstract

This methodological research develops an analytic method called the "comparative self-controlled case series" (CSCCS). The objective is to capture the beneficial aspects of the comparative new user cohort method and the self-controlled case series in a single methodological approach. The rationale is that within-person fixed effects and between-group differences can be accounted for in a single analysis. The method runs a self-controlled case series (SCCS) analysis on a new user cohort of treatment cases and a new user cohort of comparator cases and then computes the ratio of rates as the effect estimate. The treatment and comparator groups are balanced by propensity score matching before the self-controlled case series analyses are run. The CSCCS is demonstrated by comparing celecoxib and non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) for risk of gastrointestinal (GI) bleeding and myocardial infarction (MI) in osteoarthritis patients. In preliminary results, the CSCCS effect estimate for risk of GI bleeding is similar the risk estimate from the comparative cohort analysis. The MI risk estimates differ between the two methods.

Introduction

Observational healthcare data is abundant and regularly used to generate evidence on the safety of medical products in the real world context. The comparative new user cohort and SCCS are two analytic methods of empirically demonstrated high performance in risk measurement using observational data[1].

The new user cohort method evaluates and compares the risk of a health outcome in two treatment or exposure groups. The two groups represent treatment options for a population defined by a health condition, much like in a randomized controlled trial. Unlike a randomized trial, however, selection effects drive treatment assignment and can confound the association between the treatment group and outcome. Propensity scores, the conditional probability of treatment assignment given all pre-treatment information, can be used to mitigate these biases in order to estimate the true association[2].

The SCCS is a method to measure the association between transient exposures and health outcomes in only those patients who have experienced the outcome of interest. By comparing unexposed and exposed time at risk within individuals, this relative incidence measure is implicitly controlled for fixed covariate effects. This method is statistically efficient thereby requiring smaller sample sizes and allows controlling for age variation in baseline incidence[3].

The objective of this work is to design and implement a method that combines the advantages of the new user cohort and SCCS designs. Although the comparability of treatment groups in new user cohorts is vastly improved by propensity score methods which can account for thousands of covariates unfortunately absent from these are relevant individual and contextual factors of a patient's life that may also influence health outcomes, such as genetics, socio-economic status and employment status. The SCCS controls for these factors by making within-person exposed versus unexposed comparisons. This should not discredit the bias reduction attributable to balancing observed covariates between treatment groups using propensity scores, which is critical for comparative effectiveness research. The proposed CSCCS balances two sets of cases on observed covariates and then runs two concurrent SCCS analyses, one for a treatment intervention and one for comparator intervention, and then computes the ratio of rates as the relative effect estimate. The rationale is that within-person fixed effects and between-group differences can be accounted for in a single methodological approach.

Methods

We evaluated this novel method by investigating the association of celecoxib, a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID), and non-selective NSAIDs (nsNSAIDs) naproxen, ibuprofen, and diclofenac on gastrointestinal (GI) bleeding and myocardial infarction (MI) in osteoarthritis patients in the Truven MarketScan Medicare Supplemental Beneficiaries database (MDCR). For context, a systematic review on the effects of individual NSAIDs on upper GI complications found that compared to non-use, celecoxib (RR 1.45, 95% CI 1.17-1.81), ibuprofen (RR 1.84, 95% CI 1.54-2.20), diclofenac (RR 3.34, 95% CI 2.79-3.99), and naproxen (RR 4.10, 95% CI 3.22-5.23) all increased risk[4].

The proposed method is an extension of a "comparative self-controlled cohort study", which is an extension of a SCCS. In the self-controlled cohort method, outcome risk is estimated as the incidence rate ratio of post-exposure and pre-exposure incidence rates of patients exposed to the treatment of interest[5]. Note that the self-controlled cohort method does not use an active comparator group. This design is extended to the treatment vs. comparator framework in the "comparative self-controlled cohort design" by executing a parallel SCCS on patients exposed to a comparator drug, often of the same indication, and estimating relative outcome risk as a ratio of rate ratios[7]. Similar to the new user cohort method, the covariate distribution of the treatment and comparator arms can be balanced

by propensity score matching, stratification, or weighting. In the CSCCS, parallel SCCS are executed which each produce a Poisson distributed within-person incident rate ratio, one for each of the treatment and comparator groups. The ratio of these incidence rate ratios is then taken as the between-group relative effect measure with associated confidence intervals[6,7].

The CSCCS was executed on the same propensity score-matched cases used in a comparative new user cohort study evaluation the risk of GI bleeding and MI in osteoarthritis patients. Patients were matched 1-to-1 on demographic covariates and pre-index drug and device exposures, procedure and condition occurrences, and various risk scores (e.g. Charlson Comorbidity Index[8]). Cox proportional hazards models were used to estimate relative risk in 30 days post-index. The SCCS models were specified to drug exposure and a 30-day pre-exposure risk window as covariates and to adjust for event-dependent censoring.

This study uses the CohortMethod and SelfControlledCaseSeries R packages from the OHDSI methods library[9,10].

Results

The new user cohort design found celecoxib to be associated with decreased risk of GI bleeding (RR=0.55) and MI (RR=0.96) compared to nsNSAIDs (Table 1). The SCCS analyses on balanced cases found celecoxib (IRR=2.54) and nsNSAIDs (IRR=4.47) to be associated with increased risk of GI bleeding. The ratio of the IRRs for the GI bleeding outcome (RRR=0.57) is similar in magnitude to that from the new user cohort design. For MI, the balanced SCCS analyses similarly found celecoxib (IRR=2.87) and nsNSAIDs (IRR=2.08) to be associated with increased risk. However, the ratio of the IRRs for MI (RRR=1.38) is of the opposite direction than the effect of celecoxib relative to nsNSAIDs in the new users cohort analysis. Precision estimates and empirical calibration for the RRR estimates are in the process of being calculated[10].

Table 1. Results from comparative new user cohort, SCCS, and CSSCS designs

Design	Treatment	Comp.	Outcome	Effect measure	GI Bleed β	MI β
New User Cohort	Celecoxib	nsNSAIDs	GI Bleed	RR	0.555	0.964
SCCS	Celecoxib time-at-risk	Celecoxib time not at-risk	GI Bleed	IRR	2.544	2.873
SCCS	nsNSAIDs time-at-risk	nsNSAIDs time not at-risk	GI Bleed	IRR	4.471	2.078
CSCCS	Celecoxib SCCS	nsNSAIDs SCCS	GI Bleed	RRR	0.569	1.383

*SCCS=Self-Controlled Case Series, CSSCS=Comparative Self-Controlled Case Series, RR=Relative Risk, IRR=Incident Rate Ratio, RRR=Rate of Rate Ratios, SCCS = self-controlled case series, CSCCS = comparative self-controlled case series, nsNSAID = non-selective NSAID, GI Bleed = Gastrointestinal Bleed, MI = Myocardial Infarction

Conclusion

Preliminary results are inconclusive and suggest that effect estimates from the novel CSCCS may or may not be comparable to those from comparative new user cohort studies and the following evaluation framework is in place to qualify and properly contextualize the results. Empirical calibration will be performed across negative controls on both methods to determine the null distributions against which each model's effect estimates are tested[11]. This will quantify the residual bias attributable to each model and allow for their direct comparison. We will also develop the appropriate method for error estimation and then compute coverage probability, which is the proportion of confidence intervals that include the known relative risk for each outcome (e.g. RR>1) and negative control (e.g. RR=1). The model's discriminative performance in identifying outcomes and negative control outcomes will also be tested. Lastly, we will discuss the applicability of the CSCCS model to various research tasks and elaborate on how it can contribute to those areas of research to which it is best suited.

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