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Clinical Research

Impact of Injectable Furosemide Hospital Shortage on Congestive Heart Failure Outcomes: A Time Series Analysis

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ABSTRACT

Background: Beginning in February 2012, there was a shortage of injectable furosemide in the province of Ontario, Canada. The objective of this study was to assess the effects of the furosemide shortage on heart failure outcomes in Ontario, Canada.

Methods: We determined which hospitals experienced a shortage of injectable furosemide using an online survey. We then used health administrative data to identify all patients who presented to those hospitals with congestive heart failure. Using 40 months of data from before the shortage, we determined the proportion of patients with heart failure expected to die each month. We then used time series analysis to forecast the 30-day mortality rate during the shortage period and compared it with the observed rate. Secondary outcomes included length of hospital stay, transfer to an intensive care unit, mechanical ventilation during the hospital stay, and risk of 30-day readmission for heart failure.

Results: Survey results were obtained for 82% of hospitals, 28 of which experienced a severe shortage of injectable furosemide in the

RÉSUMÉ

Contexte : Depuis février 2012, la province de l'Ontario (Canada) fait face à une pénurie de furosémide pour injection. Cette étude avait pour objectif d'évaluer les effets de la pénurie de furosémide sur la mortalité des patients atteints d'insuffisance cardiaque en Ontario.

Méthodes : Nous avons répertorié à l'aide d'un sondage en ligne les hôpitaux qui faisaient face à une pénurie de furosémide pour injection. Ensuite, à partir de données administratives sur la santé, nous avons recensé tous les patients qui avaient été hospitalisés dans ces établissements en raison d'une insuffisance cardiaque congestive. À partir des données couvrant la période de 40 mois précédant le début de la pénurie, nous avons déterminé la proportion attendue de décès chaque mois chez les patients atteints d'insuffisance cardiaque. Nous avons ensuite effectué une analyse chronologique pour prévoir le taux de mortalité à 30 jours durant la période de pénurie, que nous avons comparé au taux observé. Les paramètres d'évaluation secondaires étaient notamment la durée de l'hospitalisation, le transfert dans une unité de soins intensifs, le recours à la ventilation mécanique durant le

Sandoz Canada (Boucherville, Quebec) was the largest manufacturer of injectable medications in Canada and the sole supplier of 140 injectable drugs for the Canadian health care system.[1] Operational issues, including a slowdown in production in response to a US Food and Drug Administration warning letter in February 2012 and a fire at the Boucherville, Quebec plant in March 2012, decreased production by 74%.[2] One of the drugs in short supply was injectable furosemide, a loop diuretic that is the mainstay of treatment for patients with acute decompensated heart failure.[3]

Hospitals across Ontario have different policies regarding the stockpiling of medications considered to be of critical importance.[4] In March 2012, institutions without reserves of injectable furosemide faced critical shortages and were forced to enact policies designed to limit its use. The high prevalence of heart failure and the importance of intravenous diuretics in its acute management set the stage for potentially serious adverse outcomes.

To determine the impact of limited access to injectable furosemide on the care of patients with heart failure across Ontario, we first surveyed inpatient hospital pharmacies to identify which hospitals experienced a severe shortage. We

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year 2012. The 30-day mortality among patients presenting to these hospitals with congestive heart failure before the shortage period was 11.2%. We forecasted a mortality rate of 11.3% (95% confidence interval, 8.2-14.4) for the shortage period, which was not significantly different from the observed rate of 10.9%. Similarly, we found no significant effect of the shortage on secondary outcomes.
Conclusions: A severe shortage of injectable furosemide did not increase the risk of adverse outcomes among patients who presented to the hospital with congestive heart failure.

séjour à l'hôpital et le risque de réadmission dans les 30 jours pour cause d'insuffisance cardiaque.
Résultats : Les réponses au sondage ont été obtenues pour 82 % des hôpitaux, dont 28 qui avaient fait face à une grave pénurie de furosémide pour injection en 2012. Le taux de mortalité à 30 jours chez les patients qui avaient été hospitalisés dans ces établissements en raison d'une insuffisance cardiaque congestive avant la période de pénurie était de 11,2 %. Nous avions prédit un taux de mortalité de 11,3 % (intervalle de confiance à 95 % : de 8,2 à 14,4), valeur qui n'est pas significativement différente du taux observé de 10,9 %. De même, nous n'avons observé aucun effet significatif de la pénurie sur les critères d'évaluation secondaires.
Conclusions : La grave pénurie de furosémide pour injection ne s'est pas traduite par une augmentation du risque d'issue défavorable chez les patients hospitalisés en raison d'une insuffisance cardiaque congestive.

then assessed the effects of this shortage to test the hypothesis that heart failure outcomes would be worse during the shortage period compared with periods before.

Methods

Study design and setting

This study was conducted in 2 phases. We first identified hospitals in the province of Ontario, Canada that experienced a severe shortage of injectable furosemide by surveying inpatient pharmacies (Supplemental Appendix S1). We then conducted a cross-sectional time series analysis examining health outcomes of patients who presented to these hospitals before and during the shortage.

Survey

We distributed an online survey to inpatient pharmacies across Ontario. The purpose of the survey was to identify the hospitals that experienced a shortage of injectable furosemide in the year 2012. For those experiencing a shortage, we assessed its severity by identifying policies that were implemented to mitigate its effects and the duration those policies were in effect. Specifically, for hospitals in which there was a shortage, we asked if (1) pharmacy staff engaged with medical staff to clarify the need for injectable furosemide, (2) injectable furosemide use was limited to certain services (critical care units, coronary care units), and (3) whether equivalent oral doses were automatically substituted for injectable furosemide orders. We sent the survey link electronically beginning in August 2014, and responses were received up to June 2015. Nonresponders received specific e-mails and then telephone calls. Continued nonresponse resulted in contact with pharmacy directors and hospital administrators. The survey was conducted according to a protocol approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (No. 238-2014; approval date July 15, 2014).

Shortage definitions

Before administering the survey, we defined 3 levels of injectable furosemide shortage: no shortage, moderate shortage, and severe shortage. Hospitals that denied experiencing a shortage and enacted no measures to deal with the shortage were considered to have experienced no shortage. Hospitals that reported a shortage but engaged only in educational programs for medical staff in attempts to limit the use of injectable furosemide were considered to have experienced a moderate shortage. Hospitals that reported having a shortage and took steps to deny access to injectable furosemide through restriction of its use to certain medical services or automatic substitution policies, or both, were considered to have experienced a severe shortage. Only hospitals that experienced a severe shortage were included in the time series analysis because we hypothesized a priori that patients admitted to these institutions were more likely to be affected and because these policies allowed us to accurately identify the onset date of the shortage.

Time series analysis

Study design. After identifying hospitals that experienced a severe shortage, we conducted a retrospective population-based study using databases held at the Institute for Clinical Evaluative Sciences (ICES). We assessed the aggregated outcomes of patients admitted to those hospitals during 2 periods: before the shortage ("preshortage period," with an observation window of 40 months) and during the shortage ("shortage period," with a mean observation window of 7 months). We then used the proportions of patients experiencing outcomes during the preshortage period to forecast the proportions experiencing outcomes during the shortage period. Phase 2 of this study was also approved by the Institutional Review Board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Data sources. Data sets at ICES were linked using unique encoded identifiers, and our time series analysis was completed at the ICES Western site in London, Ontario, Canada. With a prespecified protocol, we used 5 linked health care administrative databases to ascertain patient baseline and outcome characteristics. The Ontario Registered Persons Database provides demographic and vital status information. The Ontario Health Insurance Plan database contains health

claims for both inpatient and outpatient physician services. Diagnostic and procedural information for hospitalizations are recorded in the Canadian Institute for Health Information Discharge Abstract Database, and emergency department visits are recorded in the National Ambulatory Care Reporting System. We used the Ontario Drug Benefit program to identify prescription drug use. This database contains highly accurate records of all outpatient prescriptions dispensed to individuals aged 65 years or older, with an error rate of $< 1\%$.[5] The data sets were complete for all variables used in this study (with the exception of income and rural/urban residence, with 1% missing data). All administrative codes used in this study are shown in Supplemental Table S1.

Patients. We identified individuals aged 40 years or older who had a hospital encounter for congestive heart failure defined as an emergency department visit or hospital admission at an institution identified to have experienced a severe shortage of injectable furosemide. We defined admission with heart failure using validated administrative codes that have been shown to have a sensitivity of 89.9% and a specificity of 93.5% in our data sources.[6] We considered patients to have been admitted with heart failure if these codes were found in the "main diagnosis" field of the records, meaning that heart failure was the main determinant for the duration of admission. We compared baseline characteristics of patients admitted in the final month of the preshortage period to those of patients admitted during the first month of the shortage period. Comparing subsets of the 2 periods allowed us to minimize the clustering of baseline characteristics that may have arisen from repeated admissions of individual patients.

Primary outcome. The primary outcome was the difference between the forecasted and observed proportions of patients with heart failure dying of any cause. Death is ascertained in our data sources with a sensitivity of 97.8% and a specificity of 100%.[7]

Secondary outcomes. We identified 4 secondary outcomes that could be a consequence of inadequate diuresis: length of hospital stay > 6 days (median length of stay), transfer to an intensive care unit, mechanical ventilation during the hospital stay, and risk of 30-day readmission for heart failure.

Analysis. To identify a change in outcomes associated with the shortage of injectable furosemide, we identified 3 variables: (1) the start date of the shortage, (2) the proportion of patients experiencing the outcome before the shortage, and (3) the proportion of patients experiencing the outcome during the shortage.

The shortage start date for each hospital was identified in the survey responses. Because the reported start dates were similar but not identical, we harmonized all hospitals to a common "time zero." To determine the risk of an outcome during the 2 periods (before and during the shortage), we produced plots showing the proportion of admitted patients experiencing the outcome each month for 40 months before the shortage and for a maximum of 8 months during the shortage. The use of 40 preshortage months provided enough data to produce precise forecasts of the shortage period event rates while avoiding the inclusion of more remote periods when practice patterns may not have reflected those of the shortage period. All hospitals were censored at 8 months after the shortage start date or at their specific shortage end date, whichever came first.

Statistical analyses

We conducted a time series analysis using Statistical Analysis System Econometrics and Time Series (SAS/ETS), version 9.4, software (SAS Institute, Cary, NC). Time series models were fit to the data using SAS/ETS, with the final model best fitting the data before the shortage determined based on the Bayesian information criterion. When comparing models to determine the best fit of the data, the most complex model with the most parameters will always appear to have the best fit. The Bayesian information criterion method penalizes model complexity and allowed us to select the model that maximized the likelihood while remaining parsimonious.[8]

This model was used to produce forecasts for the outcome during the shortage periods that could be compared with the true proportions that occurred during the shortage. We considered a 2-sided P value < 0.05 to be statistically significant.

Results

Survey

We sent surveys to 171 hospitals in Ontario covering approximately 18,000 inpatient beds. We received responses from 82% of hospitals, with 61 hospitals indicating that they had experienced a shortage of injectable furosemide. Of the 61 hospitals experiencing a shortage, 28 hospitals met our definition of severe shortage by limiting furosemide use to certain services or automatically substituting injectable furosemide orders with an equivalent oral dose. Two hospitals were able to purchase a limited supply of injectable furosemide from alternative manufacturers, 1 hospital made ethacrynic acid available, and 1 institution sourced bumetanide. For hospitals that were defined as having a severe shortage, the reported shortage start date ranged from February 1, 2012-May 1, 2012, and the shortage end date ranged from May 31, 2012-October 10, 2014. The differences in shortage end dates related to varying levels of success in securing alternative sources of injectable furosemide, with 2 hospitals leaving their injectable furosemide-conserving policies in place into 2014. However, the median length of the severe shortage for these hospitals was 7 months; these hospitals were the focus of our time series analysis.

Time Series Analysis

Baseline characteristics. Over the entire study period, there were 29,981 hospital encounters with heart failure among individuals aged 40 years or older (24,201 occurred during the preshortage period and 5780 occurred during the shortage period). When we compared the baseline characteristics of patients admitted in the last month of the

preshortage period with patients admitted in the first month of the shortage period, we found the groups to be well balanced (Table 1). In the last month of the preshortage period, there were 786 admissions for heart failure across the 28 hospitals. The median age of the study population was 80 years (interquartile range [IQR], 71-85 years), and 48% were women. Of the 786 admissions, 511 (65%) occurred at community hospitals, 262 (33%) occurred at teaching hospitals, and 13 (2%) occurred at rural hospitals. Many patients had coronary artery disease (80%), diabetes (56%), hypertension (85%), and baseline prescriptions for oral loop diuretics (58%).

Primary outcome. During the preshortage period, 30-day mortality among patients admitted with heart failure fluctuated between 8.2% and 14.1%, with a monthly average of 11.2% (Fig. 1). Using these data and a moving average model with lag 2, we forecasted a mortality rate of 11.2% (95% confidence interval [CI], 8.7-13.7) for the first month of the shortage period and 11.3% (95% CI, 8.2-14.4) for the entire shortage period. The observed 30-day mortality was 10.2% for the first month and 10.9% for the entire shortage period. Neither of these observed rates differed significantly from the forecasted values.

Secondary outcomes. Consistent with our primary analysis, there was no observed effect on secondary outcomes during the period of the injectable furosemide shortage (Supplemental Figs. S1-S4). Figure 2 shows the number of injectable vs oral prescriptions at 1 of the institutions that experienced a shortage from January 2011-June 2012. The number of doses was relatively stable from January 2011-January 2012, with a higher number oral furosemide prescriptions. However, after the onset of the shortage and start of the automatic substitution policy on February 27, 2012, there was a sharp increase in oral furosemide prescriptions and a sharp decrease in injectable furosemide prescriptions.

Table 1. Baseline characteristics among patients with heart failure who presented across 28 different hospitals in Ontario, Canada with a severe shortage of intravenous furosemide, categorized into before shortage and shortage periods

Patient baseline characteristic	Before shortage (n = 786)	Shortage (n = 828)	*P* value
Demographics			
Age, y	80 (71-85)	80 (72-86)	0.37
Women	379 (48.2%)	428 (51.7%)	0.14
Income, lowest quintile	210 (26.7%)	223 (26.9%)	0.75
Rural residence*	40 (5.1%)	64 (7.7%)	0.03
Primary care visits in past y	13 (6-22)	12 (6-21)	0.69
Previous hospitalization (in past y)	< 6	< 6	0.61
Comorbidities (in past 5 y)			
Atrial fibrillation	253 (32.2%)	264 (31.9%)	0.89
Cancer	286 (36.4%)	296 (35.7%)	0.78
Chronic liver disease	28 (3.6%)	26 (3.1%)	0.59
Chronic lung disease	211 (26.8%)	236 (28.5%)	0.43
Chronic kidney disease	284 (36.1%)	284 (34.3%)	0.42
Chronic obstructive pulmonary disease	134 (17.0%)	155 (18.7%)	0.36
Coronary artery disease	546 (69.5%)	559 (67.5%)	0.38
Diabetes mellitus	441 (56.1%)	471 (56.9%)	0.74
Hypertension	664 (84.5%)	702 (84.8%)	0.86
Peripheral vascular disease	40 (5.1%)	50 (6.0%)	0.36
Stroke	49 (6.2%)	51 (6.2%)	0.95
Ventricular arrhythmia	31 (3.9%)	24 (2.9%)	0.23
Procedures (in past y)			
Cardiac catheterization	95 (12.1%)	90 (10.9%)	0.42
Coronary angiography	93 (11.8%)	88 (10.6%)	0.42
Coronary artery bypass	12 (1.5%)	18 (2.2%)	0.34
Coronary revascularization	39 (5.0%)	47 (5.7%)	0.51
Dialysis	125 (15.9%)	125 (15.1%)	0.64
Percutaneous coronary intervention	28 (3.6%)	31 (3.7%)	0.84
Outpatient oral medications†			
Angiotensin-converting enzyme inhibitor	270 of 673 (34.4%)	264 (31.9%)	0.27
Angiotensin- receptor blocker	74 (9.4%)	56 (6.8%)	0.04
β-blocker	441 (52.3%)	449 (54.2%)	0.42
Calcium-channel blocker	265 (33.7%)	281 (33.9%)	0.92
Insulin	113 (14.4%)	124 (15%)	0.72
Loop diuretic	453 (57.6%)	499 (60.3%)	0.27
Oral hypoglycemic agent	189 (24.0%)	186 (22.5%)	0.43
Potassium-sparing diuretic	98 (12.5%)	106 (12.8%)	0.82
Thiazide diuretic	103 (13.1%)	111 (13.4%)	0.85
Nonsteroidal anti-inflammatory drug	50 (6.4%)	55 (6.6%)	0.80
Statin drug	442 (53.7%)	445 (53.7%)	0.98

Data are presented as number (%) except for age and primary care visits, which are presented as median ± interquartile range.

*Location of residence with a population size < 10,000 persons.

†Outpatient oral medications filled in the past 180 d was assessed in patients > 65 years of age.

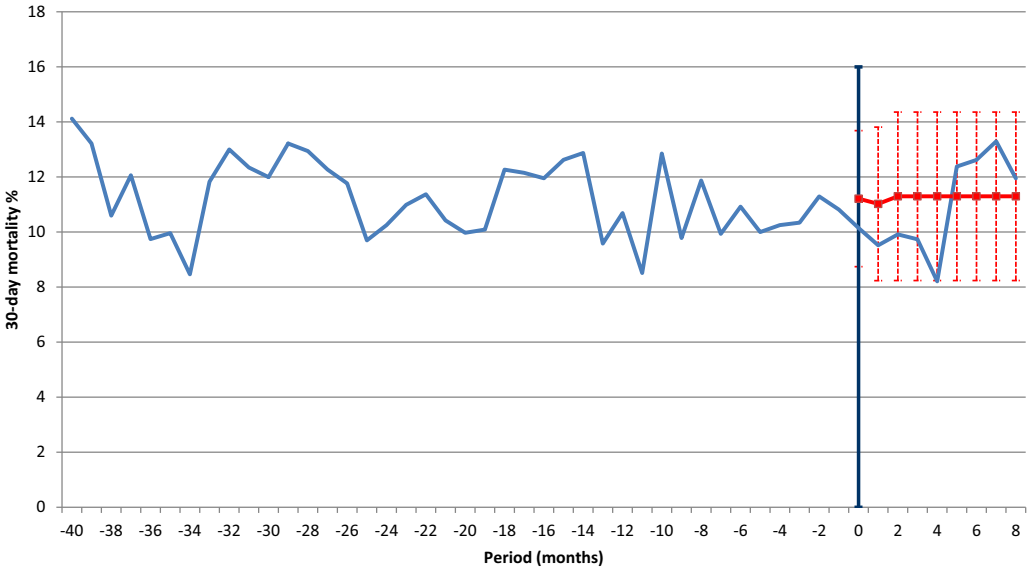
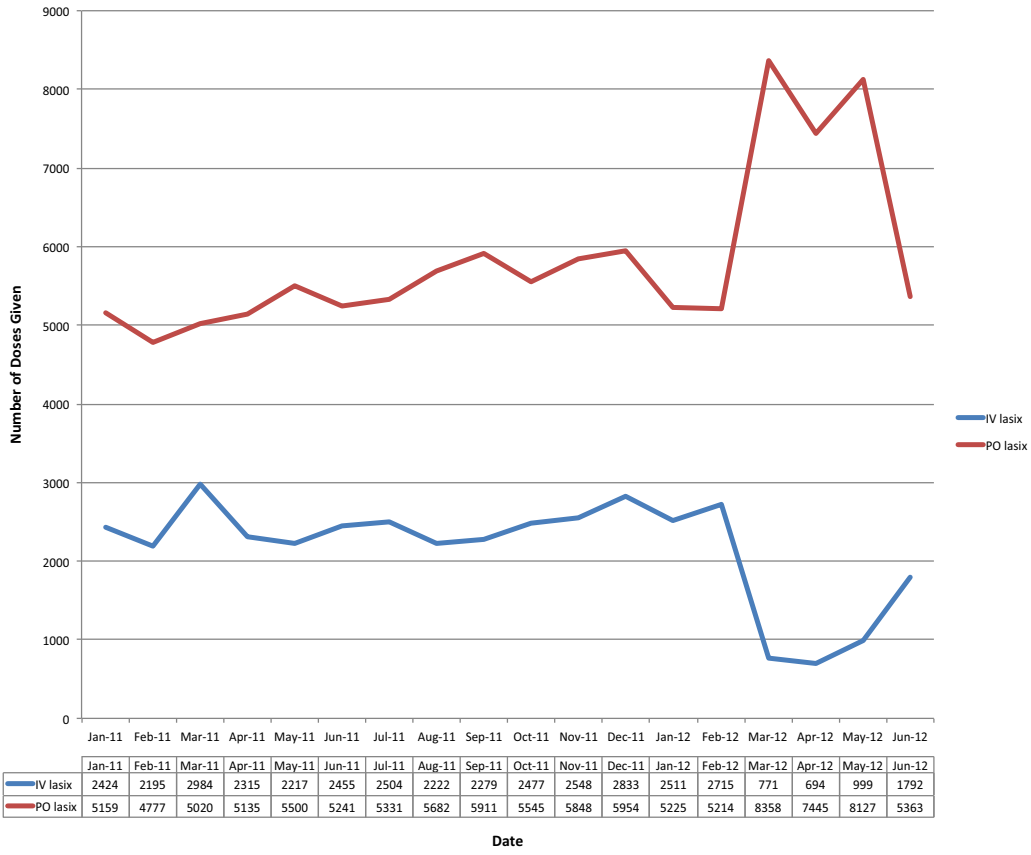


Figure 1. Thirty-day mortality among patients presenting to the hospital with congestive heart failure before and after the onset of a severe furosemide drug shortage across 28 hospitals in Ontario, Canada. The **red lines** represent the predicted percentages and their 95% confidence intervals defined by a moving average with lag 2 model.



	Jan-11	Feb-11	Mar-11	Apr-11	May-11	Jun-11	Jul-11	Aug-11	Sep-11	Oct-11	Nov-11	Dec-11	Jan-12	Feb-12	Mar-12	Apr-12	May-12	Jun-12
IV lasix	2424	2195	2984	2315	2217	2455	2504	2222	2279	2477	2548	2833	2511	2715	771	694	999	1792
PO lasix	5159	4777	5020	5135	5500	5241	5331	5682	5911	5545	5848	5954	5225	5214	8358	7445	8127	5363

Figure 2. Intravenous furosemide vs oral furosemide prescriptions at London Health Sciences Centre, London, Ontario, Canada from January 2011-June 2012.

Discussion

In this retrospective population-based study, we found that the injectable furosemide shortage was not associated with an increase in the risk of adverse clinical events among patients with heart failure. We hypothesized that limited access to a key therapy like injectable furosemide would result in a higher risk of mortality. Furthermore, because this drug is the cornerstone of treatment for volume overload, we also expected patients to have outcomes related to inadequate diuresis. In particular, we speculated that readmission to the hospital would be an important marker of underdiuresis during the initial admission. However, we observed no significant differences in mortality or any measure of morbidity.

Our study has a number of strengths. First, we achieved an 82% response rate for our survey, giving us confidence that we ascertained the majority of hospitals that experienced a severe shortage of injectable furosemide during the period of interest in the province of Ontario, Canada. Second, the risks of mortality we observed align with previous research, including a study by Jong et al.,[9] who reported a 30-day case mortality of 11.6% for heart failure admissions in Ontario. Third, we compared outcomes for hospitals experiencing a severe shortage to their own outcomes before the shortage. This removed the influence of hospital-specific characteristics that could have confounded the analysis. Fourth, because of our access to Ontario's health administrative data, we were able to analyze close to 25,000 admissions for heart failure, which resulted in forecasts with narrow confidence intervals. Finally, the assessment of heart failure and death in our data sources is reliable.[7] Although our definitions of hospital length of stay, intensive care unit admission, and mechanical ventilation have not been validated, they are linked to hospital and physician remuneration and are likely to be reasonably accurate.

Our study also has some limitations. We relied on pharmacy staff members to tell us if there was a shortage and how severe it was. Although most of the time staff accessed archived documents and protocols to answer those questions, there is no way to be absolutely certain of the accuracy of their responses. Erroneously including a hospital that truly had no shortage in our analysis would dilute the effect and bias our results toward the null.[10] Furthermore, because our study makes inferences about individual-level outcomes based on an exposure measured at the population level, 2 important issues should be considered. First, relationships between population-level exposures and individual-level outcomes can be influenced by a number of unmeasured confounders, producing associations that would not exist had exposures been measured at the individual level. However, this "ecologic fallacy" is less likely to have affected our findings because of the before/after nature of our study in which our exposed group also served as our control group. Second, our study was based on an assumption that some patients in need of injectable furosemide would not receive it during the shortage period. Although we have data from 2 hospitals showing a sharp decline in actual injectable furosemide use (Fig. 2), these data were not available for all hospitals in our study, and it does not mean needy patients went without this drug. Even hospitals truly experiencing a severe shortage may have been able to provide adequate diuresis to their patients with heart failure by diverting furosemide from other applications or providing alternative therapies; in this scenario, a severe shortage of injectable furosemide at the hospital level would not accurately reflect what happened at the patient level. Finally, our use of administrative databases meant that some clinically relevant data was not available. Although patient characteristics were well balanced across the 2 periods, we did not have access to clinical or echocardiographic measures of heart failure severity. We also did not have information on measures such as daily urine output, which may have identified an effect of the shortage. However, the clinical relevance of such an outcome is much lower than the outcomes we assessed.

Despite the limitations, if our study is considered to have accurately shown that a shortage of injectable furosemide had no significant effect on the outcomes of heart failure admissions, it implies that more judicious use of this more expensive, more invasive form of furosemide could be studied further. Injectable furosemide in our jurisdiction is 38-fold more expensive than an equivalent oral dose ($0.76 for 20 mg of injectable furosemide; $0.02 for 40 mg of oral furosemide) and this does not include the costs of the intravenous equipment or the additional nursing time. Although the absolute difference in cost is small, furosemide is used frequently. Furthermore, the use of injectable furosemide usually requires hospital admission, so our findings may provide some support for an outpatient management strategy using oral furosemide for decompensated heart failure. Although the literature is rich with assessments of diuretic strategies for decompensated heart failure, they have focused on the inpatient dosing and administration of injectable furosemide or the use of ultrafiltration.[11,12] No studies have evaluated the role for oral furosemide in patients with decompensated heart failure, partly because this patient population is frequently sick enough to warrant admission for reasons other than injectable diuretics but also because of well-established beliefs in the diminished bioavailability of furosemide in the setting of volume overload,[13] which are not supported by the literature.[14-17] Although our study does not directly inform this issue, our findings could support the careful development and study of an oral furosemide—based outpatient management strategy for decompensated heart failure.

Conclusions

In conclusion, we found no significant differences in the outcomes of patients admitted with heart failure during a shortage of injectable furosemide compared with outcomes that occurred before the shortage.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2017.09.003.