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Correlates and Economic Outcomes of Inpatient Intravenous Chlorothiazide Use - A Retrospective Study

Jane Chang, PharmD[1#], Jordan Theriault, PharmD[1#], Jayashri Sankaranarayanan, MPharm PhD[1,2*], Nicholas Tessier, PharmD, BCPS, MBA[2]

[1]Department of Pharmacy Practice, School of Pharmacy, University of Connecticut, Storrs, CT, USA
[2]Department of Pharmacy Services, Hartford Hospital, Hartford, CT, USA

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***For Correspondence**

Jayashri Sankaranarayanan, MPharm PhD, Associate Professor, School of Pharmacy, University of Connecticut, Storrs, CT, USA, Tel: 402-321-3777.

E-mail: jsankara@live.com

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#Authors Equally Contributed and PharmD Candidates during the conduct of the study.

ABSTRACT

Objectives: The hospital study objectives were 1) to evaluate frequency of appropriate/inappropriate chlorothiazide (IVCTZ) use as per hospital protocol criteria and 2) to compare estimated IVCTZ costs between appropriate and inappropriate IVCTZ use patients.

Methods: This is a 2-year (2012-2014) retrospective study. Patient data (age, hospital-LOS, urine-output (24 hour pre-, post-IVCTZ), service-unit (ICU/other), IV-loop-diuretic and IVCTZ dose, frequency, duration) were collected from the hospital's Sunrise-Clinical-Manager database. IVCTZ initiation was "appropriate" if patients had: 1) received high-dose IV loop-diuretics and 2) received at least two oral thiazide doses before IVCTZ, when on other oral medications.

Results: Majority (80%, 56/70) of patients received IVCTZ "inappropriately", 82% had not received high-dose IV loop-diuretics, 53% had not received at least two oral thiazide doses despite being on oral medications, and none qualified for "appropriate" group when 24 hour pre-IVCTZ urine- output (<480 ml/day) and other criteria considered. The greater two-year IVCTZ costs in the inappropriate versus appropriate ($84, 840 vs. $56, 160) group suggest missed IVCTZ cost-saving opportunities.

Conclusions: Hospital payers and providers efforts to promote appropriate IVCTZ use by re-evaluating the protocol inclusion-criteria of urine-output and maximizing high-dose loop-diuretic use before initiating IVCTZ in eligible patients could have a considerable impact on the total cost of health-care.

INTRODUCTION

Chlorothiazide (IVCTZ, brand name Diuril), is the only thiazide diuretic that is available as an intravenous (IV) formulation. The current United States Food Drug Administration (USFDA) approved indications of IVCTZ are hypertension and edema resulting from heart failure. According to the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines of heart failure, loop diuretics are the drug of choice for fluid retention because thiazides have a weaker diuresis response [1]. Loop diuretics act by inhibiting the sodium, potassium, and chloride co-transporter in the thick ascending Loop of Henle. Despite loop diuretics being first line agents of therapy for fluid retention, they may have inadequate response in patients. Prolonged treatment of these diuretics can lead to renal adaptation in the form of hypertrophy and hyper function of the distal tubule cells. Renal adaptation can limit the effects of loop diuretics by increasing sodium uptake and aldosterone secretion, which causes fluid retention [2]. Thiazides may be needed to enhance the diuretic effect in these patients. Thiazides inhibit the sodium and chloride co-transporters in the convoluted distal tubule resulting in an increased excretion of sodium, chloride, and

fluids. Observational studies suggest using thiazides when patients on loop diuretics exhibit renal adaptation [3]. Further, the ACCF/AHA heart failure guidelines suggest thiazide diuretics in mildly fluid overloaded patients with heart failure and concurrent hypertension. The guidelines recommend an IVCTZ dose of 500 mg to 1000 mg per day used concurrently with loop diuretics [1].

Current literature

A review of the current literature found three relevant studies on the use of thiazides. A recent systematic review analyzed 22 observational and 7 randomized studies on thiazide diuretics (including IVCTZ) in combination with loop diuretics for patients with decompensated heart failure. The authors suggest the benefits of combined diuretics may include greater fluid loss, symptomatic improvement, and shorter hospital length of stay. The authors supported IVCTZ dosing recommended by the ACCF/AHA Heart Failure guidelines of 500 mg to 1000 mg once or twice daily [2].

A retrospective study of 82 heart failure patients was conducted at The Ohio State University's Werner Medical Center in 2014. This study compared the efficacy of oral and IV thiazide diuretics in combination with IV furosemide therapy [3]. The study included a furosemide total daily dose of greater than or equal to 160 mg, with a 25 mg median dose of oral hydrochlorothiazide, or a 500 mg median dose of IVCTZ. The combination diuretic therapy has a synergistic effect in volume overloaded patients, generating a greater urine output. Previous studies have suggested a class effect, due to the outcomes seen in the use of multiple thiazide agents [2]. The results showed an increase of urine output 24 hours after a dose of oral hydrochlorothiazide or IVCTZ. However, IVCTZ produced a greater urine output compared to the oral hydrochlorothiazide. The authors recommended considering the use of oral thiazide diuretics as a cost efficient therapy option and called for further studies related to the cost of therapy.

One budget impact study conducted in 132 patients in a Maryland hospital analyzed the cost reduction for hospitals by transitioning four near bioequivalent IV medications to the oral formulation. The authors concluded chlorothiazide conversion from IV to PO had the potential to reduce drug expenditure and suggested "focusing on drugs with high savings per interruption, such as levetiracetam and chlorothiazide" [4].

Study hospital policy

Considering the poor response to loop diuretics as monotherapy and the high cost of IVCTZ, the study hospital developed a protocol to guide the appropriate add-on use of IVCTZ. The protocol required a poor response to loop diuretics given as either intermittent dosing or continuous infusion. Next, if the patient was able to ingest oral medication, two doses of add-on oral thiazide diuretics concurrently with loop diuretics should be used before considering add-on IVCTZ. The large price difference between the IVCTZ and the oral thiazide formulations can lead to an excessive increase in hospital budget. Further, oral formulations have less cost in terms of administration and maintenance of an IV line [4]. Therefore, unless a substantial urine output increase is necessary, it is more cost effective to choose the oral thiazide versus IVCTZ.

Study rationale and objectives

Current guidelines and literature suggest equivalent efficacy of concurrent IVCTZ and oral thiazides each with loop diuretics in edema [2]. A review of the literature showed that retrospective studies evaluating the appropriate versus inappropriate use of IVCTZ and associated drug costs are limited [2-4]. Therefore, the purpose of this retrospective study is to evaluate the appropriateness of the IVCTZ use in the study hospital from a payer perspective. This retrospective analysis reviewed the use of IVCTZ in the hospital over a two year period from July 2012 to July 2014. The objectives of this study were 1) to evaluate the appropriateness of IVCTZ use and 2) to compare estimated IVCTZ costs based on dosing, frequency, and duration of treatment in the appropriate and inappropriate use groups.

METHODS

Study design

This study was designed as a retrospective observational study to evaluate the appropriateness of the IVCTZ and to estimate the potential cost savings of an IVCTZ protocol implemented in the study hospital.

Setting

The teaching hospital in the study is located in the New England region of Northeastern United States. It is a tertiary care hospital with 867 beds with an annual inpatient volume of approximately of 42,000 patients.

Data sources

The data of the study population were acquired from the all scripts Sunrise Clinical Manager (SCM) database of medical records. The Institutional Review Board at the study location approved this study using de-identified patient data as "exempt" research not involving human subjects.

Inclusion criteria

All patients between the ages of 18-88 receiving IVCTZ from July 31, 2012 to July 31, 2014 were included.

Exclusion criteria

Patients having only one-time dose order of IVCTZ from July 31, 2012 to July 31, 2014 were excluded. Most patients were excluded because they only received one IVCTZ dose or because the order for IVCTZ was placed, but no dose was administered and further data on these patients was not available.

Study sample rationale

Based upon this study's inclusion and exclusion criteria, 70 out of all 335 patients receiving an order for IVCTZ during the study period, July 31, 2012 to July 31, 2014 were included in the study.

Study variables

Data on variables collected from the hospital SCM database on the 70 included patients were gender (male or female), age (years), hospital location when IVCTZ was administered (ICU or step down), hospital length of stay (days), and indication of the IVCTZ. Total loop diuretic dose (mg) and urine output (ml/day) 24 hours before IVCTZ dose (pre-chlorothiazide) were collected. IVCTZ dose (mg), number of doses per day (1, 2, 3, 4), duration of therapy (days) and urine output (ml/day) 24 hours after IVCTZ dose (post-chlorothiazide) were collected.

The first dependent variable of IVCTZ use was defined based on the hospital protocol. The IVCTZ administration was defined as "appropriate" i) if the pre-chlorothiazide urine output was less than 480 ml per day, ii) if patients were not capable of taking oral medications based on not taking other oral medications, and iii) if the patient received two doses of oral thiazide diuretics in combination of loop diuretics. As per the study hospital criteria, the IVCTZ administration in a patient was defined as "not appropriate" i) if pre-chlorothiazide urine output was greater than 480 ml per day and/or ii) if patients were capable of taking oral medications based on taking other oral medications intake but were given less than two doses of oral thiazides.

The second dependent variable was costs of IVCTZ therapy in the "appropriate" and "not appropriate" groups. These cost estimates could show the potential cost-savings from avoiding its use outside of the hospital protocol and indicate further evaluations of IVCTZ use with respect to changes in protocol. Drug cost was obtained using the average wholesale price (AWP) per drug unit obtained from the Red Book [5]. Amongst all IVCTZ products, lowest AWP per drug unit was considered to reflect costs that are more likely to resemble hospital costs for IVCTZ.

Statistical analysis

The patient characteristics for the two groups of patients (appropriate and inappropriate) were evaluated with descriptive statistics. The patient variables age (years), loop diuretic dose (mg), IVCTZ dose (mg), frequency, and pre and post chlorothiazide urine outputs (mL) were considered as continuous variables. The difference between the 24 hour post-chlorothiazide and 24 hour pre-chlorothiazide urine output (one of the hospital protocol criteria for IV to oral conversion) was also computed for the two groups as a continuous variable. These variables were reported with their Mean (± standard deviation), Median, the 25th percentile, and 75th percentile. Gender (male/female), location at dose administration, other oral medication intake (yes/no), and oral thiazide attempts (one or more) were considered categorical variables that were reported as frequencies of patients having that characteristic. Further, the frequency of patients with difference in urine output between 24 hour post-IVCTZ and 24 hour pre-IVCTZ greater than 480 ml/day (predefined from the hospital protocol) were also computed for appropriate and inappropriate patient groups as a categorical variable.

In univariate analyses, the two patient groups were compared using Fisher's exact test statistics for significant differences in proportions of categorical variables (because of small cell sizes across both groups) and using Wilcoxon rank sum tests (as the variables do not fit the normality assumption) for significant differences in continuous variables. Cost analyses were carried out using micro-costing procedures at the medication level for cost saving estimations. The average first day cost was evaluated by multiplying the unit drug cost by the dose and the frequency of IVCTZ used in the first 24 hours. Overall, the average cost of treatment included the dose, frequency, and duration of therapy. Because of the variability in medical conditions of patients in both groups, the cost analyses including average cost of hospital stay was considered unreliable and was limited to IVCTZ costs. Further, cost analysis comparing the savings that could be made when patients who received IVCTZ had received at least 2× oral doses of CTZ would be of interest.

The uncertainty of the unit drug cost on the outcome of potential drug costs was also tested. For this purpose, a sensitivity analysis was conducted by varying unit drug costs by ± 20%. Costs were estimated from using Microsoft Excel version 2010. Data were analyzed using the statistical program SAS version 9.3 (Copyright, SAS Institute Inc, Cary, North Carolina).

RESULTS

Seventy patients were found eligible and evaluated for the frequency of appropriate IVCTZ use and for IVCTZ cost estimates. **Table 1** describes the basic patient characteristics by appropriateness (as per earlier defined criteria but not using the urine output criteria) of IVCTZ use. Pre-chlorothiazide dose urine output was not considered to determine appropriateness of IVCTZ therapy, because 84% (59/70) of patients had a pre-chlorothiazide urine output greater than one liter. Few patients (6%, 4/70)

had 24 hour pre-IVCTZ urine output lesser than 480 ml/day. No patient qualified for "IVCTZ appropriate use" group when 24 hour pre-IVCTZ urine output (<480 ml/day) and other criteria were considered. Most patients in the inappropriate (75%, 42/56) versus appropriate (36%, 5/14) group had urine output difference (between 24 hour post-IVCTZ and 24 hour pre-IVCTZ) greater than 480 ml/day. Thus, IV chlorothiazide was administered inappropriately and appropriately in 80% (56/70) and 20% (14/70) of patients, respectively.

Table 1. Characteristics of patients receiving intravenous chlorothiazide.

Patient Characteristics (Mean ± SD, Median [P25, P75] unless otherwise specified)	Appropriate Use (n=14, 20%)	Inappropriate Use (n=56, 80%)	P-value ¶
Age (Years)	71.71 ± 12.29; 71.00 (66, 83)	66.61 ± 12.51; 69.00 (59.5, 69.5)	0.191
Gender, n (%)			1.000
Male	7 (50%)	30 (54%)	
Female	7 (50%)	26 (46%)	
Patient Location, n (%)			0.260
ICU*	12 (86%)	53 (95%)	
Step-down	2 (14%)	3 (5%)	
Average Hospital Length of Stay (Days)**	43.42 ± 23.65; 34.5 (28,58)	29.07 ± 15.63; 27 (17.5, 39.5)	0.031¶
Indication, n (%)			0.750
Heart Failure	7 (50%)	27 (48.2%)	
Hypertension	0 (0%)	3 (5.4%)	
Heart Failure and Hypertension	4 (28.6%)	15 (26.8%)	
General or Pulmonary Edema	2 (14.3%)	3 (5.4%)	
Other***	1 (7.1%)	8 (14.3%)	
24 hours Pre-Chlorothiazide Urine output (ml/ day; Median [P25, P75])	2561.57 ± 1450.58; 2765 (1139, 3695)	2782.07 ± 1747.22; 2602.50 (1430, 3878.5)	0.814
24 hours Post-Chlorothiazide Urine output (ml/ day	2990.43 ± 1694.37; 2672 (2082, 3840)	4469.68 ± 2354.13; 4335 (2470, 6527.5)	0.037¶
Difference in Pre-Post Chlorothiazide Urine output	425.86 ± 978.17; (-104, 975)	1687.61 ± 1884.10; (386.50, 2893)	0.017¶
1 day Urine Response Greater than 480 ml/day, n (%)	5 (36%)	42 (75%)	0.009¶
Criteria for IVCTZ use			
IV Furosemide Daily Dose (mg)	706.43 ± 285.48; 710 (520, 960)	294.23 ± 207.60 296 (135,440)	<0.0001¶
IV Bumetanide Daily Dose (mg)	5.79 ± 17.90; 0 (0,0)	1.64 ± 5.13 0 (0,0)	0.462
High dose diuretic dose not received, n (%)	0 (0%)	50 (89%)	<0.0001¶
Patients on Oral Medications so eligible for oral thiazides, n (%)	14 (100%)	49 (87.5%)	0.331
Did not receive 2 Doses of Oral Thiazides, n (%)	0 (0%)	26 (46%)	<0.0001¶
Patients Not Receiving Oral Thiazides****, n (%)	0 (0%)	7 (13%)	0.331

Note: *: Consist of cardiac, medical and surgical; **: Skewed from outlier number of days; ***: Encompasses indications such as ascites, cardiomyopathy and combination indication CHF/Pulmonary Edema, HTN/ Pulmonary Edema, CHF/Edema; ****: If the patient was not on oral medications, then the patient was not required to receive 2 doses of oral thiazides; ¶p: <0.05 is statistically significant

Both groups were similar in terms of gender, indication, and location of IVCTZ administration. Sixty-five patients were administered IVCTZ in the intensive care unit (ICU) and of those patients; sixty-three were in the cardiac ICU (data not shown). A majority of the patients in the appropriate (57%) and inappropriate (50%) group received IVCTZ for heart failure. A third of the patients had a combined indication of heart failure and hypertension, which is a common indication for IVCTZ (29% in the appropriate group and 27% in the inappropriate group). Thus, about 79% and 75% of patients receiving IVCTZ had heart failure or heart failure with hypertension. There were no significant differences in the urine output in the 24 hours before IVCTZ administration in both groups. Patients in the appropriate versus the inappropriate IVCTZ group had significantly higher diuretic (IV furosemide 706.43 ± 285.48 vs. 294.23 ± 207.60, p<0.0001, not IV bumetanide) dose. Further, significantly more patients in

the inappropriate versus appropriate group (50/56, 89% vs. 0/14, 0%, p = <0.0001) received IVCTZ without fulfilling the protocol criteria of "receiving prior high dose loop diuretic".

In the inappropriate group, even though 87.5% (49/56) were capable of oral intake (the second criteria for receiving oral vs. IVCTZ) as they were on other oral medications, 53% (26/49, data derived from Table 1 not shown) did not receive at least two attempts of oral thiazides (the third criteria for receiving oral vs. IVCTZ). However, all patients in the appropriate versus the inappropriate IVCTZ group fulfilled at least two criteria. First, all patients in the appropriate versus the inappropriate IVCTZ group were on other oral medications (100% vs. 88%). Second, significantly all patients in the appropriate versus the inappropriate IVCTZ group had received two oral thiazide doses (100% vs. 41%, p = 0.0002). Third, significantly fewer patients in appropriate versus the inappropriate group (36% vs. 75%, p = 0.0094) had a one-day urine output greater than 480 ml after the first IVCTZ dose and continued to receive IVCTZ instead of being switched to oral thiazide.

Table 2 demonstrates the estimation of IVCTZ costs in both the appropriate and inappropriate groups by the average daily cost and the average cost of treatment. Majority of the patients received 500 mg of IVCTZ (71% in the appropriate group and 55% in the inappropriate group) and received twice a day dosing (71% in the appropriate group and 53% of the inappropriate group). Considering the dose and frequency of IVCTZ, the average one day cost in the inappropriate group was $443.57 (SD ± 246.37) per patient. The total daily costs of IVCTZ of all the inappropriate group patients were significantly higher than the appropriate group patients ($24,840 vs. $8,640), p = 0.0219). In two years the total cost of IVCTZ treatment was $84,840 in the inappropriate group versus the $56,160 in the appropriate group.

Table 2. Estimation of use and cost in appropriate and inappropriate IV chlorothiazide use groups.

Characteristics* - n (%), unless otherwise specified	Appropriate Use (n=14, 20%)	Inappropriate Use (n=56, 80%)	P-value**
Chlorothiazide Strength (mg)			0.011**
250	2 (14.29)	25 (44.64)	
500	10 (71.43)	31 (55.36)	
1000	2 (14.29)	0	
Administration Frequency (# of doses/day)			0.647
1	0	8 (14.29)	
2	10 (71.43)	30 (53.57)	
3	2 (14.29)	10 (17.86)	
4	2 (14.29)	8 (14.29)	
Duration of Therapy in Days (Mean ± SD)	5.86 ± 7.53	3.25 ± 2.54	0.547
Average Cost for Single Day of Treatment (Mean ± SD)	$617.14 ± 261.46	$443.57 ± 246.37	0.022**
Total Single Day Cost	$8,640.00	$24,840.00	0.022**
Average Cost for Treatment (Mean ± SD)	$4,011.43 ± 6,848.94	$1,515.00 ± 1,415.16	0.069
Total for Treatment Cost	$56,160.00	$84,840.00	0.069
Sensitivity Analyses: at ± 20% of drug cost estimates			
Total for Single Day Cost + 20%	$10,260.00	$29,497.50	0.022**
Total for Single Day Cost - 20%	$6,840.00	$19,665.00	0.022**
Total treatment Cost + 20%	$66,690.00	$100,747.50	0.069
Total treatment Cost - 20%	$44,460.00	$67,165.00	0.069

Note: *: Note all Costs are in 2014 US dollars and are cost of IV chlorothiazide; **: p<0.05 is statistically significant.

The sensitivity analysis showed a higher treatment cost with a drug unit cost 20% higher than the average wholesale price (AWP) and lower cost with a drug unit cost 20% less. Using 20% higher drug unit cost, the total first day IVCTZ costs were $10,260 in the appropriate and $29,497.50 in the inappropriate group, respectively (p = 0.0219). Using the 20% lower drug unit cost, the total first day IVCTZ costs were $6,840 in the appropriate and $19,665 in the inappropriate group (p = 0.0219). For the total treatment cost for all patients with 20% higher than the unit drug cost, the appropriate group cost $66,690 and the inappropriate group cost $100,747.50. The total treatment cost with the 20% less than AWP shows $44,460 in the appropriate group and $67,165 in the inappropriate group.

DISCUSSION

Recent studies have focused on the use of chlorothiazide in heart failure patients [2,3,6,7]. These studies have shown that add-on thiazides work in combination with loop diuretics to improve patient's volume overload status. One recent study reported

efficacious and safe sequential nephron blockade with either metolazone or chlorothiazide in acute decompensated heart failure (ADHF), renal dysfunction, and diuretic resistance [6]. The studies also suggest that while all thiazides work to increase urine output, using oral thiazides before IV thiazides could save costs. To the authors' knowledge, this is one of first retrospective studies evaluating the appropriateness and cost of IVCTZ in a hospital setting in recent times. Therefore most findings of the current study are reported for the first time in literature. In the current study the overall majority (80%, 56/70) of the patients received IVCTZ "inappropriately" as they did not meet at least one of the three eligibility criteria (high diuretic dose, on other oral medications, received two oral thiazide doses) stated in the hospital protocol.

Only 20% of the study patients fulfilled all three criteria for IVCTZ use. First, 89% (50/56) of patients did not meet the study hospital protocol criteria of receiving the first IVCTZ dose only if they had received high dose loop diuretics (receiving greater than 480 mg of furosemide or greater than 24 mg of bumetanide for 24 hours). Second, patients who were able to take oral medications should have been received at least two doses of oral thiazides before moving on to IVCTZ. Further, 53% (26/49) patients from the inappropriate group were eligible to receive oral thiazides as they were receiving other oral medications at the time of IVCTZ dosing; however, they did not receive oral thiazides.

Several elements need to be considered to improve the effectiveness of the study hospital's protocol to support appropriate IVCTZ use. Though the hospital IVCTZ protocol calls for initial urine output less than 480 ml before adding on IVCTZ to high dose loop diuretic use, only four out of the seventy patients included in the current study had a 24 hour pre IVCTZ dose, urine output less than 480 ml as specified in the protocol. Twenty one out of the seventy patients (30%) in the study had urine outputs that were lower than 480 ml after twenty-four hours of IVCTZ initiation. This further suggests the need for refinement and guidance on the dosing, duration, continuing and discontinuing use of IVCTZ in the protocol. One study stated that IVCTZ should only be considered in "… gross fluid overload refractory to optimized doses of…" IV loop diuretics [2]. However, in the current study, the mean daily dose of furosemide was 294 mg (less than 480 mg) and bumetanide was about 2 mg (less than 24 mg) in patients falling into the inappropriate group. This suggests that majority of patients in the current study received non- optimized doses of loop diuretics. The current study authors' agree that the patient's in the inappropriate group should have received maximum dose limit of their IV loop diuretics before IVCTZ was added. To limit the use of the expensive IVCTZ, the protocol criteria of maximizing loop diuretic doses needs to be reevaluated and implemented in the future. Although, the majority of patients in the inappropirate vs. appropriate group received it in once or twice daily frequency (71% vs. 68%) and 250-500 mg daily dose (100% vs. 88%) as per clinical guidelines [4], the duration of IVCTZ was lower (3 vs. 6 days). However, the protocol does not include any guidance on duration of IVCTZ use. One way to prevent IVCTZ overuse is to keep orders from lingering longer than necessary. Therefore, such guidance on duration of IVCTZ use could be made available in the hospital protocol in the future with providers' input.

The current study findings suggest that in 80% of patients, who inappropriately received IVCTZ, there are opportunities to realize savings on drug costs with appropriate use. IV chlorothiazide is a costly add-on to loop diuretic treatment in heart failure. The first day of IVCTZ costs were significantly higher in the inappropriate versus the appropriate group patients ($24, 840 vs. $8,640). Considering the entire length of therapy in each patient, IVCTZ costs were higher in the inappropriate versus the appropriate group patients ($84, 840 vs. $56,160). These findings that have not been reported before suggests there are opportunities to save on costs through appropriate use of IVCTZ.

Several limitations may have affected the study findings. One limitation is that the majority (265/335) patients were excluded because they only received one dose of IVCTZ or they might have had an order for IVCTZ, but never received a dose. However, more details on these patients to consider their inclusion and eligibility for oral doses were not available; therefore, authors were unable to include them for further analyses. Second, the study only considers the loop diuretic dose that was received twenty-four hours before IVCTZ initiation. Patients may have received high dose loop and other class diuretics just outside that period that may have affected their response; however, such data was not available to the authors. Third, despite collecting recorded objective measures of response of urine output, authors were unable to access subjective measures of clinical status, such as dyspnea, that may have dictated the treatment course.

Evaluation of the sustainability of the response was not possible even though the 24 hour follow-up duration helped minimize the influence of confounders in assessing the impact of appropriate and inappropriate use of IVCTZ on urine output. There was no documentation to evaluate reasons as to why IVCTZ was administered despite patients having high urine output that did not qualify them to receive IVCTZ. It is possible that the medical teams needed higher urine output in patients than specified in the protocol with high dose loop diuretics alone. Thus, patients in the inappropriate group continued to receive IVCTZ even though they could probably have received oral thiazides. This may be because clinicians continued using IVCTZ perceiving it as more effective than oral thiazides in improving the patients' symptoms faster and possibly reducing their overall hospital LOS. However, documentation was not available in the medical records on why medical teams may have needed higher urine output than that specified in the hospital protocol or used IVCTZ rather than oral thiazides. Perhaps in the future, such data needs to be collected at the point of patient-care. Fourth, comorbidities were not considered in this study as it was not possible to collect accurate data from the in-patient records. Future studies will need to consider patient comorbidities and the need for add-on thiazide therapy. Fifth, although most patient characteristics (age, gender, and patient location) were similar between the appropriate and in appropriate use groups, the current study findings are inherently limited by its retrospective design, small sample size and lack of

randomization. Sixth, although this investigation includes pharmacoeconomic analyses; unlike earlier studies, the current study' cost findings could be an underestimate. This is because the study was unable to consider additional costs of IVCTZ use from IV placement, maintenance, drug administration, monitoring, oral thiazide use, and hospital acquired infections, adverse events, and increased hospital LOS, which all affect hospitalization and IVCTZ costs. Though considering additional costs beyond IVCTZ costs was beyond the scope and objective of the study, such costs need to be considered in future evaluations. On other hand, the current study estimates could be an overestimate of the drug costs because the authors used AWP from red book which are considerably higher than what hospitals pay for drugs. However, to get a realistic estimation of drug costs, knowing that a hospital purchaser buys at low costs, the lowest price of all available IVCTZ products was used and sensitivity analyses was carried out to address issues of over estimation of costs. Despite the limitations, the study provides payers and providers real-world evidence on potential opportunities for refining the protocol, and monitoring implementation of the protocol to improve the quality of IVCTZ use and realize cost savings in hospitals.

CONCLUSIONS

In summary, this is one of the first few retrospective studies to evaluate appropriateness of IVCTZ initiation and estimation of cost savings in a north-eastern teaching hospital in the United States. Majority (80%, 56/70) of patients received IVCTZ "inappropriately", 82% had not received high-dose IV loop-diuretics, and 53% had not received at least two oral thiazide doses despite being eligible as they were on other oral medications. Further, none qualified for "appropriate" group when 24 hour pre-IVCTZ urine-output (<480 ml/day) and other criteria were considered. The greater two-year IVCTZ costs in the inappropriate versus appropriate ($84, 840 vs. $56,160) group suggest missed cost-saving opportunities. Hospital payers and providers need to re-evaluate the protocol inclusion-criteria of urine-output and maximize high-dose loop diuretic and oral thiazide use before initiating IVCTZ therapy for more cost efficient diuresis in the health-care systems.

DECLARATION OF INTEREST SECTION

At the time of conduct of the study, all authors reported no source of funding, or any financial/other relationships (such as consultancies, employment, expert testimony, honoraria, speakers' bureaus, retainers, stock options or ownership).

AUTHORS' CONTRIBUTIONS

All authors conceived and designed the study. JS gained ethical approval. NT and JS got access to the data for the study. JC and JT collected data under supervision of NT and JS. JS, JC, and JT carried out quality audit and analyses of the data. JC and JT were involved in writing and revising the initial draft of the manuscript under the supervision of JS. All authors (JC, JT, and NT led by JS) had an opportunity to review and revise the final paper for intellectual content.

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