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Comparison between Torsemide Infusion Versus Intermittent Boluses and Their Impact-On Thoracic Fluid Content in Acute Decompensated Heart Failure Critically Ill Patients

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ABSTRACT

Background: It is still debatable whether loop diuretics should be given intravenously as boluses or continuously by infusion while treating acute decompensated heart failure (ADHF).

Objective: We aimed to evaluate the differences between the two administration routes on the thoracic fluid content (TFC), renal functions, urine output, electrolytes, haemodynamic parameters, echo cardiographic parameters, incidence of atrial fibrillation and NYHA class.

Patients and methods: Eight hundred thirty patients admitted to the Critical Care Medicine Department, Faculty of Medicine Helwan University, Egypt with acute decompensated heart failure (ADHF) were enrolled in the study; thirty patients were excluded due to EF>40%, myocardial infarction within 30 days and baseline creatinine level > 4 mg/dl. Torsemide 200 mg per day was given to the remaining 800 patients who continued in the study after 1:1 randomization to either continuous intravenous infusion (group I, 400 patients), or twice equal intermittently daily doses (group II, 400 patients). No subsequent dose titration done all over the first 4 days.

Results: The delta TFC all through the four days were all statistically significant giving the superiority of the infusion route over the twice daily regimen. While urine output was increased all through the four days, with significant statistical difference in favor of the infusion group but creatinine level, urea level, creatinine clearance were all non-significant statistically when comparing the two groups. The NYHA class started to be significant statistically from the third and fourth days in favor of infusion group.

Conclusions: We concluded that torsemide infusion when compared to the torsemide twice equal dose in ADHF, causes more decrease in TFC, symptomatic improvement with non-significant nephrotoxic effects.

Keywords: Torsemide, ADHF, TFC.

INTRODUCTION

Heart failure is a major public health issue across the world, with high morbidity, value, and expense. In affluent nations, it affects 1-2% of individuals, with the frequency rising to roughly 8.4% in the population over 70 [(1)].

Patients with heart failure frequently take loop diuretics to treat congestion symptoms, increase exercise tolerance, and lower mortality risk [(2)]. As one of the many negative effects of using diuretics, hypotension [(3)], may develop as a result of the fast intravascular volume reduction and direct venodilatation brought on by diuresis [(4)]. The use of loop diuretics results in the activation of the sympathetic and renin-angiotensin-aldosterone nerve systems. Loop diuretics can cause hypokalemia as a side effect that is associated with the use of loop diuretic administration, and neurohormonal activation can trigger cardio-renal syndrome and renal hypo-perfusion caused by hypotension [(5)].

The most effective way to provide intravenous loop diuretics is still up for debate, however standard delivery methods include intravenous boluses or continuous infusions. Theoretically, the use of continuous infusion may be more advantageous in the counterintuitive rise in systematic vascular resistance that is more closely linked to intravenous boluses, along with enhanced neuro-hormonal activation and lower cardiac parameters [(6)]. Continuous loop diuretics infusion increases diuretic effectiveness and reduces diuretic toxicity by utilising lower dosages in post-cardiac surgery patients with heart failure. According to **Felker *et al.*** [(7)] there is no discernible difference between continuous infusion and boluses in terms of effectiveness and change from baseline renal functions.

Impedance cardiography (IC) is a non-invasive technique for ongoing hemodynamic monitoring that is secure, repeatable, and appropriate for a variety of heart failure patients [(8)]. One of the important hemodynamic characteristics that IC evaluates is thoracic fluid content (TFC). TFC and chest wall impedance are inversely correlated, meaning that when TFC rises, chest wall impedance falls. Chest intravascular and extravascular fluid components and TFC are correlated [(9)].

Regarding lowering TFC, clinical improvement, and safety, we aimed to evaluate intravenous torsemide treatment as a continuous infusion with intermittent boluses in patients with acute decompensated heart failure (ADHF).

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PATIENTS AND METHODS

This is a prospective randomized trial comparing continuous vs intermittent intravenous torsemide administration in individuals with ADHF diagnosis and volume overload. We included patients admitted to the Critical Care Department, faculty of Medicine' Hospitals, Helwan University in Egypt from June 2020 to June 2022 with volume overload.

Volume overload was characterised as having at least one clinical sign and at least one symptom (dyspnea at rest, orthopnea, or peripheral edoema) (rales of pulmonary congestion, jugular vein dilatation, or a third heart sound).

Inclusion criteria:

Patients under the age of 18, those with heart failure who had preserved EF (EF > 40%), those who had a recent myocardial infarction within 30 days of admission, those with serum creatinine levels > 4.0 mg/dl, and those who required renal replacement therapy during their hospital stay were all excluded from the study.

Each patient underwent a complete clinical examination that focused on their clinical history, vital signs, urine output, renal functions, electrolytes, incidence of atrial fibrillation, and echo-cardiographic parameters. It also included a lengthy discussion of their medical history.

On admission and every day for the first four days following admission, tests for the complete blood count, liver function, cardiac biomarkers, serum creatinine and urea, sodium, and potassium were conducted. The Cockroft & Gault equation was used to determine creatinine sodium clearance (Crcl) [(10)].

All patients were randomized in a 1:1 ratio into two groups:

Group I patients received torsemide infusion 8 mg/hr (200 mg/day), and Group II patients received torsemide at a dose of 100mg every 12hrs (200 mg/day). No subsequent dose titration of torsemide was done in the first four days.

Based on the current standard recommendations for ADHF, the use of additional agents to control ADHF (ACE-I/ARBS, Digoxin, and/or nitrates) was decided, but no other forms of diuretic agents were permitted during the research period.

Electrical Cardiometry was used to measure the amount of thoracic fluid (ICON cardiotronics, inc., La Jona, CSA 92, 307 Osypka Medical GmbH, Berlin, Germany).

The device emits electrical current with high frequency-low constant amplitude that is interpreted by the device. This current is very low and is not harmful to patients. The measurement unit is $K\Omega^{-1}$; Normal value range is 25-35 $K\Omega^{-1}$ [(11)]. The gadget generates a high frequency, low constant amplitude electrical current that the gadget interprets. Patients are not harmed by this extremely low current. $K\Omega^{-1}$; is the measuring unit, and the typical value range is 25 to 35 $K\Omega^{-1}$ [(11)].

Electrical cardiometry was performed using four electrodes, two of which were placed on the left side of the neck (the first electrode about 5 cm above the root of the neck and the second electrode at the root of the neck), the other two electrodes were placed on the chest (one was placed on the level of xiphoid on the left side and the other placed 5 cm lateral to the previously placed electrode at level of anterior axillary line).

Before taking measures, the equipment was provided patient data such as gender, weight, height, and age. TFC was measured on admission, then every 24 hours over the next three days, for a total of four days. ΔTFC was estimated as the decline in TFC with time. ΔTFC1 reflects the drop during the first 24 hours (ΔTFC 1 = TFC at admission - TFC after 24 hours). ΔTFC4 denotes the reduction on the fourth day following admission (ΔTFC 4 = TFC on admission - TFC after 4 days).

Every patient had their weight loss (weight reduction during the first 24 hours = body weight on admission - body weight after 24 hours) and hourly urine output measured in milliliters per kilogram body weight (ml/kg/hr).

Serum electrolytes, renal function, acute kidney damage (defined as an acute rise of serum creatinine > 0.3 mg/dl within 48 hours) [(12)], hypokalemia (defined as serum K+ level < 3.5 meg/L), and the requirement for vasoactive and/or inotropic support were all considered as adverse events.

Using a 17-inch, high-resolution TFT LCD screen on a General Electric Vivid S6 ultrasound system, the echocardiographic parameters (LVEDD, LVESD, and EF%) were assessed.

Ethical consent:

The study was authorised by Helwan University's Ethical Institutional Review Board. All study participants provided written informed permission after being informed of our research's goals. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical Methods

Using the statistical package for social science (SPSS 26), data were prospectively collected and coded prior to analysis. The normal distribution of various dependent variables in relation to their independent variables was studied, and the appropriate analysis was carried out depending on the type of data obtained for each parameter. For numerical data with a parametric distribution, the mean, standard deviation (± SD), and range were used. For non-parametric data,

the median and interquartile range (IQR) were used. Proportion and frequency for non-numerical information. The statistical significance of the difference between the means of the two study groups was evaluated using the Student T-test.

The correlation between two qualitative variables was investigated using the chi-square test. When the predicted count is less than 5 in more than 20% of cells, Fisher's exact test was employed to investigate the association between two qualitative variables.

The statistical significance of the difference between two means assessed twice for the same research group was evaluated using a paired t-test. The statistical significance of the difference between a qualitative variable recorded twice for the same research group was evaluated using the McNemar test. P value ≤ 0.05 was regarded as significant.

RESULTS

A Total of 830 patients were enrolled in the study with exclusion of 30 patients, 21 patients were excluded for preserved ejection fraction (> 40%), 4 patients for serum creatinine > 4 mg/dl, and 5 for recent myocardial infarction within 30 days of admission.

Table (1) showed the demographic data when compared between both groups as regards sex, age, weight, height and body mass index that all were non-significant statistically. Except weight in the fourth day which was statistically significant.

Table (1): Demographic Data in each group of the study all over the 4 days

		Group		Test of significance		
		Torsemide infusion	Torsemide bid			
Sex	Male	209(52.25%)	226(56.56%)	X^2=1.456	0.228	NS
	Female	191(47.75%)	174(43.5%)			
Age (Years)		48.2 9± 9.2	48.26 ± 8.93	t = 0.051	0.960	NS
Weight-post-1 (kg)		81.57 ± 6.15	81.6 ± 6.42	t = -0.073	0.942	NS
Weight-post-2		80.57 ± 6.15	81.38 ± 6.4	t = -1.837	0.067	NS
Weight-post-3		80.45 ± 6.12	80.95 ± 6.42	t = - 1.122	0.262	NS
Weight-post-4		79.6 ± 6.16	80.59 ± 6.44	t = -2.212	0.027	S
Height (cm)		168.59 ± 7.43	168.51 ± 7.26	t = 0.15	0.878	NS
BMI – post-1 (kg/m^2)		28.84 ± 3.05	28.9 ± 3.42	t = - 0.301	0.764	NS
BMI – post-2		28.48 ± 3.03	28.83 ± 3.4	t = - 1.515	0.130	NS
BMI – post-3		28.44 ± 3.04	28.67 ± 3.4	t = -1.018	0.309	NS
BMI – post-4		28.14 ± 3.01	28.55 ± 3.4	t = -1.786	0.074	NS

Table (2) showed the thoracic fluid content (TFC) all through the four days of the study in favor of the torsemide infusion group when compared to the boluses group (bid) together with Δ TFC in the 4 days of the study with a highly significant statistical difference p-value < 0.001.

Table (2): Thoracic fluid content in each group with delta thoracic fluid content during the 4 days study

	Group		Student t-test		
	Torsemide infusion	Torsemide bid			
	Mean ± SD	Mean ± SD	t	p-Value	Sig.
TFC-pre	82.66 ± 5.04	82.82 ± 5.01	- 0.429	0.668	NS
TFC-post-1	75.61 ± 5.53	77.87 ± 5.05	- 6.055	<0.001	S
TFC-post-2	68.99 ± 5.82	72.5 ±5.39	- 8.854	<0.001	S
TFC-post-3	62.26 ± 5.91	66.85 ± 5.93	- 10.970	<0.001	S
TFC-post-4	53.49 ± 5.9	60.87 ± 6.9	- 16.272	<0.001	S
Δ TFC1	20.01 ± 2.25	4.94 ± 1.12	101.864	<0.001	S
Δ TFC2	14.45 ± 3.43	10.32 ± 2.32	14.230	<0.001	S
Δ TFC3	20.41 ± 4.92	15.97 ± 3.73	13.631	<0.001	S
Δ TFC4	29.18 ± 5.8	21.94 ± 5.44	18.175	<0.001	S

Table (3) showed that electrolytes serum potassium started to be significantly statistically decreased from the second, third and fourth day when compared between both groups, which was more evident in the infusion group, while serum sodium was more evident in decreasing in the infusion group, starting only from the third and fourth day with a statistical significant p-value. Urine output was increased more in the infusion group rather than in the boluses group when compared between each other with a highly significant statistical difference all through the 4 days, while creatinine urea and creatinine clearance were all statistically insignificant when compared between both groups.

Table (3): Electrolytes, urine output, creatinine, urea and creatinine clearance in both-groups during the 4 days of the study

	Group		Student t-test		
	Torsemide infusion	Torsemide bid			
	Mean ± SD	Mean ± SD	t	p-Value	Sig.
Serumpotassium –pre	5.01 ± 0.57	5.02 ± 0.57	-0.186	0.552	NS
Serumpotassium-post-1	4.66 ± 0.58	4.72 ± 0.53	-1.599	0.110	NS
Serumpotassium-post-2	4.24 ± 0.57	4.35 ± 0.53	-3.016	0.003	S
Serumpotassium-post-3	3.84 ± 0.59	4.05 ± 0.52	-5.622	<0.001	S
Serumpotassium-post-4	3.5 ± 0.71	3.77 ± 0.51	- 6.235	<0.001	S
Serumsodium-pre	137.01±8.35	127.31±4.99	-0.619	0.536	NS
Serumsodium-post-1	135.32±8.23	135.58±4.94	-0.596	0.585	NS
Serumsodium-post-2	132.52±8.04	1433.42±4.81	-1.617	0.056	NS
Serumsodium-post-3	130.93 ± 7.94	132.15 ± 4.85	-2.622	0.009	S
Serumsodium-post-4	128.16 ± 7.92	130.14 ± 4.7	-4.307	<0.001	S
Uop-pre	752.38±145.69	751 ± 145.87	0.133	0.394	NS
Uop-post-1	943.83±181.71	852.03±165.25	6.643	<0.001	S
Uop-post-2	1054.58±197.15	4852±189.37	4.852	<0.001	S
Uop-post-3	1243±227.24	1182.232.77	3.677	<0.001	S
Uop-post-4	1889.81±339.2	1416±274.51	21.717	<0.001	S
Creatinine - pre	0.85 ± 0.21	0.85 ± 0.20	0.090	0.929	NS
Creatinine-post-1	0.88 ± 0.21	0.89 ± 0.21	- 0.695	0.487	NS
Creatinine-post-2	0.92 ± 0.22	0.95 ± 0.19	-1.475	0.141	NS
Creatinine-post-3	0.93 ± 0.22	0.95 ± 0.22	-1.483	0.139	NS
Creatinine-post-4	0.96 ± 0.23	0.98 ± 0.23	-1.031	0.303	NS
Urea-pre	29.33 ± 7.29	29.41 ± 7.82	-0.102	0.919	NS
Urea-post 1	30.96 ± 7.32	31.3 ± 7.12	-0.431	0.666	NS
Urea-post 2	32.73 ± 7.75	33.01 ± 8.10	-0.377	0.706	NS
Urea-post 3	33.86 ± 8.23	34.38 ± 9.97	-0709	0.478	NS
Urea-post 4	34.9 ± 8.62	35.44 ± 8.22	-0.720	0.472	NS
Creatinine clearance-pre	105.3 ± 16.4	105.26 ± 13.04	0.031	0.975	NS
Creatinineclearance-post-1	103.3±16.02	102.54±12.88	0.732	0.464	NS
Creatinineclearance-post-2	101.49±15.95	100.67±12.75	0.806	0.421	NS
Creatinineclearance-post-3	100.24±15.82	99.5±12.63	0.730	0.466	NS
Creatinineclearance-post-4	98.07±15.55	97.42±12.38	0.658	0.511	NS

Table (4) showed the risk factors from smoking, Diabetes mellitus, hypertension, dyslipidemia together with the etiology of cardiomyopathy which were all statistically non-significant.

Table (4) Risk factors and etiology of cardiomyopathy in each group of the study

		Group		Test of Significance		
		Torsemide infusion	Torsemide bid			
		N (%)	N (%)	Value	p-Value	Sig.
Smoking	No	120 (30%)	132 (33%)	X^2=0.834	0.361	NS
	Yes	280 (70%)	268 (67%)			
DM	No	152 (38%)	148 (37%)	X^2=0.85	0.77	NS
	Yes	248 (62%)	252 (63%)			
HTN	No	170 (42.5%)	184 (46%)	X^2=0.993	0.319	NS
	Yes	230 (57.5%)	216 (545)			
Dyslipidemia	No	207 (51.75%)	216 (54%)	X^2=0.406	0.524	NS
	Yes	193 (48.255%)	184 (46%)			
Idiopathic	No	192 (48%)	188 (47%)	X^2=0.08	0.777	NS
	Yes	208 (52%)	212 (53%)			
Ischemic	No	208 (52%)	212 (53%)	X^2=0.08	0.777	NS
	Yes	192 (48%)	188 (47%)			

Table (5) showed the hemodynamic parameters represented in the mean arterial blood pressure (mmHg), which started to be significant statistically in favor of the torsemide infusion versus the torsemide bid from the third and fourth days. The systolic blood pressure, which run in the same results like the mean arterial blood pressure to be in favor of the torsemide infusion group starting from the third and fourth days. While the diastolic blood pressure and heart rate were all non-significant statistically when compared between both groups.

Table (5): Hemodynamic parameters in each group through the 4 days study

	Group		Student t-test		
	Torsemide infusion Mean ± SD	Torsemide bid Mean ± SD			
MAP-pre	100.29 ± 8.3	100.35 ± 9.18	t=-0.086	0.932	NS
MAP-post-1	106.4 ± 8.63	106.31 ± 9.46	t=0.130	0.897	NS
MAP-post-2	113.09 ± 9	112.27 ± 9.79	t=1.223	0.222	NS
MAP-post-3	118.74± 9.45	117.26 ± 10.04	t=2.152	0.032	S
MAP-post-4	130.62 ± 10.4	125.23 ± 10.81	t=7.186	<0.001	S
SBP-pre	139.85 ± 12.35	140.29 ± 13.46	t=0.485	0.628	NS
SBP-post-1	146.59 ± 12.31	146.9 ± 14.22	t=0.323	0.747	NS
SBP-post-2	153.91 ± 12.93	152.18 ± 14.15	t=1.813	0.070	NS
SBP-post-3	161.61 ± 13.57	158.32 ± 14.16	t=3.365	0.001	S
SBP-post-4	177.78 ± 14.92	164.67 ± 14.07	t=12.777	<0.001	S
DBP-pre	79.92 ± 11.46	79.77 ± 10.65	t=0.189	0.850	NS
DBP-post-1	85.69 ± 11.84	85.41 ± 10.88	t=0.351	0.725	NS
DBP-post-2	92.05 ± 12.36	91.72 ± 11.47	t= 0.400	0.689	NS
DBP-post-3	96.66 ± 12.98	96.11 ± 11.96	t=0.621	0.535	NS
DBP-post-4	106.32 ± 14.27	104.91± 13.17	t=1.457	0.146	NS
HR-pre	89.89 ± 16.79	90.03 ± 17.67	t=-0.119	0.905	NS
HR-post-1	93.8 ± 16.55	93.69 ± 17.51	t=0.091	0.927	NS
HR-post-2	97.4 ± 16.47	97.38 ± 17.4	t=0.023	0.982	NS
HR-post-3	98.39 ± 16.6	98.51 ± 17.52	t=-0.096	0.924	NS
HR-post-4	101.34 ± 17.14	101.55 ± 18.02	t= -0.168	0.866	NS

* Chi-Square test of significance (X^2). * Student t-test of significance (t).

Table (6) showed the incidence of atrial fibrillation when compared between both groups with non-significant statistical difference all through the 4 days of the study.

Table (6): Atrial fibrillation in each group during the 4 days of the study

		Group		Test of Significance		
		Torsemide infusion	Torsemide bid			
		N (%)	N (%)	Value	p-Value	Sig.
AF-pre	No	346 (86.5%)	352 (88%)	X^2=0.405	0.525	NS
	Yes	54 (13.5%)	48(12%)			
AF-post-1	No	346 (86.5%)	352 (88%)	X^2=0.405	0.525	NS
	Yes	54 (13.5%)	48 (12%)			
AF-post-2	No	346 (86.5%)	352 (88%)	X^2=0.405	0.525	NS
	Yes	54 (13.5%)	48 (12%)			
AF-post-3	No	346 (86.5%)	352 (88%)	X^2=0.405	0.525	NS
	Yes	54 (13.5%)	48 (12%)			
AF-post-4	No	326 (81.5%)	336 (84%)	X^2=0.876	0.349	NS
	Yes	74 (18.5%)	64 (16%)			

Table (7) showed the echocardiographic parameters when compared between both groups during the study 4 days, represented in the left ventricular end diastolic diameter, which improved more in the torsemide group of bid more than the infusion group started from the second, third and fourth days while the left ventricular end systolic diameter improved in the torsemide bid group starting from the first, second and third days and became non-significant in the fourth day. Also the ejection fraction was non-significant statistically when compared between both groups from the first, second and third days with a statistical significant improvement in favor of the torsemide infusion group in the fourth day of study.

Table (7): Echocardiographic parameters in each group in the 4 days of the study

	Group		Student t-test		
	Torsemide infusion	Torsemide bid			
LVEDD-pre	62.24 ± 3.44	62.29 ± 3.5	t=0.224	0.823	NS
LVEDD-post-1	61.96 ± 3.47	61.66 ± 3.55	t=1.199	0.231	NS
LVEDD-post-2	61.01 ± 3.46	60.41 ± 3.56	t=2.408	0.016	S
LVEDD-post-3	59.52 ± 3.4	58.79 ±3.46	t=3.004	0.003	S
LVEDD-post-4	53.35 ± 3.05	52.66 ± 3.2	t=3.145	0.002	S
LVESD-pre	44.13 ± 3.8	44.31 ± 3.52	t=-0.696	0.487	NS
LVESD-post-1	43.78 ± 3.88	42.28 ± 3.26	t=5.924	<0.001	S
LVESD-post-2	43.09 ± 3.84	41.04 ± 3.33	t=8.048	<0.001	S
LVESD-post-3	41.95 ± 3.8	39.62 ± 3.37	t =9.186	<0.001	S
LVESD-post-4	37.44 ± 3.4	37.5 ± 3.22	t = -0.265	0.791	NS
EF-pre	37.62 ± 1.8	37.6 ± 1.81	t=0.118	0.906	NS
EF-post-1	37.79 ± 1.96	37.65 ± 1.95	t=1.01l	0.313	NS
EF-post-2	38.41 ± 1.99	38.24 ± 2	t=1.250	0.212	NS
EF-post-3	39.37 ± 2.05	39.09 ± 2.07	t=1.896	0.58	NS
EF-post-4	43.42 ±2.25	42.99 ± 2.32	t=2.676	0.008	S

* Chi-Square test of significance (X^2). * Student t-test of significance (t).

Table (8) showed the improvement in NYHA class started from the third and fourth days in favor of the torsemide infusion group when compared to the torsemide bid group with a highly significant statistical difference p-value <0.001.

Table (8): NYHA class in each group during the 4 days study.

		Group		Chi-Squre test		
		Torsemide infusion	Torsemide bid			
		N (%)	N (%)	X^2	p-Value	Sig.
NYHA Class-pre	III	0(0%)	0(0%)			
	IV	400 (100%)	400(100%)			
NYHA Class-post-1	III	0(0%)	0(0%)			
	IV	400 (100%)	400(100%)			
NYHA Class-post-2	III	0(0%)	0(0%)			
	IV	400 (100%)	400(100%)			
NYHA Class-post-3	III	56 (14%)	0(0%)	60.215	<0.001	S
	IV	344 (86%)	400 (100%)			
NYHA Class-post-4	III	400(100%)	260 (65%)	169.69	<0.001	S
	IV	0(0%)	140(35%)			

DISCUSSION

Recent recommendations for loop diuretics to alleviate pulmonary congestion, lower left ventricular pressures, and lessen peripheral fluid retention [13-15]. The most effective way of delivery is still unknown, and several research on the subject have produced inconsistent findings. However, continuous infusion has shown to be a good form of administration [16, 17, 18]. While, others did not [7, 19]. Subjective efficacy end points as symptomatic improvement was reported in many studies and others had more objective end points as B type-natriuretic peptide (BNP) [30].

There were no studies that compared invasive pulmonary artery catheter (PAC) or non-invasive intravenous (IC) delivery techniques on the lung water objectively. The effectiveness and safety of intravenous infusion of torsemide in patients hospitalised by ADHF were compared, with the efficacy being predominantly assessed by the TFC assessed by ICON. Thoracic impedance cardiography was used to confirm the diagnosis and assessment of therapy response for heart failure [20, 21]. IC calculates TFC, which was successfully employed in ADHF patients and was found to be equivalent to PAC for the assessment of cardiac output [22-24]. It is one of the hemodynamic measures that represents interstitial, intra-vascular, and intra-alveolar fluid inside the thorax [32, 33], and pulmonary capillary wedge pressure [25], which have both been linked to blood BNP levels in patients with heart failure [26].

With similar dosages of torsemide given over the course of the first four days as a continuous infusion or intermittent boluses, 800 patients were hospitalised with a primary diagnosis of ADHF. Regarding demographic information, co-morbidities, the cause of heart failure, and other clinical and laboratory results, there was no statistically significant difference between study groups.

As regards our study, TFC was decreased significantly during the four days with more improvement in the torsemide continuous infusion when compared to the intermittent bolus twice daily, with also improvement in the NYHA class starting from the third and fourth days of study. Continuous infusion led to more obvious body weights reduction especially in the fourth day when compared to the intermittent boluses dose with a significant statistical difference. This matches with previous studies, which demonstrated that increased diuresis was related with continuous infusion of loop diuretics [16, 27, 28].

Dose trial [7] was one of the largest prospective trials with 308 patients evaluating the administration of the loop diuretic furosemide but no prior trials on torsemide, no significant difference was found in the subjective patients' global assessment of symptoms, no difference between the two administration methods regarding treatment failure, and no difference between the two methods of administration regarding adverse events, change in body weight and net fluid loss were also similar in both groups, which is different from our study results where body weight was significantly statistically in favor of the continuous infusion group in the fourth day of the study. At the same time, the TFC was also in favor of the continuous infusion all through the four days of the study. Also in dose trial [7], poor responders allowed by dose investigators to increase 50% of the dose of loop diuretic after 48 hrs, which did not occur in our study. Higher needs for increasing the dose is the attributed cause of lack of efficacy of infusion method and the higher total dose of loop diuretic they reported in the boluses group [7]. Absence of loading doses is the leading cause of lack of preferential diuretic effect of infusion in the dose trial, which was concluded by some other investigators [29-31], which is also different from our results as we did not give bolus dose before starting the torsemide infusion and the results were positive in the side of the torsemide infusion versus the bolus doses, which were same dosage in both groups.

In contrast to study **Pang *et al.*** [32], ours demonstrated a positive relationship between the diuretic impact and the reduction of heart failure symptoms. **Dikshit *et al.*** [3] hypothesised that ventilation may also play a role in the clinical improvement brought on by the loop diuretic torsemide in ADHF.

In our study relative decrease in serum potassium and serum sodium was evident in the infusion group more than the bolus group with significant statistical difference starting from second, third and fourth days of the study as regard the potassium level and from the third and fourth days for the sodium level. While, creatinine, urea and creatinine clearance were statistically insignificant when compared between both groups all through the four days of the study. This is contradictory to **Palazzuoli *et al.*** [21] who found that continuous infusion of a loop diuretic led to an increase in serum creatinine, a decrease in eGFR, a decrease in potassium, and no discernible change in blood sodium. On the contrary of our study, dose trial [14] stated that serum creatinine level change from base line to 72 hours between the two administration methods. **Palazzuoli *et al.*** [21] stated that the intra-vascular volume depletion is the explained cause for deterioration in kidney function caused by the more potent diuretic effect. Early intra vascular volume depletion caused by large volume dieresis this is corrected by plasma refill from the extra vascular space [33], but this was not consistent in other studies [16-32, 34] but consistent with our study results.

As urine output was increased all through the four days of the study with more prominent effect in the continuous infusion group in comparison with the intermittent bolus group with more increase in mean arterial pressure starting from the third and fourth days of the study with significant statistical difference in favor of the continuous infusion group. Also, the

systolic blood pressure started to increase from the third and fourth days of the study in the continuous infusion group with a significant statistical difference when compared to the intermittent boluses group, while the diastolic blood pressure and heart rate were all non-significant statistically all through the study days.

All dose trial [7] was on the contrary of our results as regards the incidence of hypotension and the need of inotropic and/or vasopressor support in our study as no hypotension had occurred during the study.

Many studies runs in favor of the continuous infusion method as regards urine output and blood pressure in hemodynamically unstable patients or borderline hemodynamics rather than the intermittent boluses due to more predictable urine output [32-34].

Echocardiographic parameters, the left ventricular end diastolic diameter was statistically significant from the second, third and fourth days of the study where the left ventricular end systolic diameter was statistically significant starting from the first, second and third days and non-significant in the fourth day. While the ejection fraction was only significant statistically in the fourth day of the study in favor of the continuous torsemide infusion.

Atrial fibrillation incidence was non-significant statistically during the four days study when compared the continuous infusion of torsemide versus the intermittent boluses doses.

CONCLUSION

Continuous infusion of torsemide carries a more favorable outcome in patients complaining of ADHF in comparison with intermittent boluses doses of torsemide as regards more diuresis, improving thoracic fluid content, NYHA class without deterioration in the renal function or creatinine clearance with improving mean arterial blood pressure and echocardiographic parameters.

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