Original Research Article

Etilefrine could improve response to standard medical therapy in chronic hepatitis C Egyptian patients with cirrhotic refractory ascites: A Randomized Pilot Study

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Abstract

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Ascites is a frequent complication of cirrhosis that accounts for over 75% of episodes of ascites. Patients with cirrhotic ascites have marked splanchnic vasodilation and arterial hypotension with subsequent activation of vasoconstrictive and anti-natriuretic mechanisms. One of the most serious complications in cirrhotic patients with ascites is the occurrence of refractoriness that is the inability to resolve ascites by the standard medical treatment. The aim of this study is to evaluate the effects of etilefrine on systemic hemodynamics, renal function and control of ascites in chronic hepatitis C (CHC) patients with cirrhotic refractory ascites receiving standard medical treatment (SMT) with low sodium diet and maximal diuretic doses of 160 mg/day of furosemide and 400 mg/day of spironolactone. A total of 50 CHC patients with cirrhotic refractory ascites were prospectively studied after 1 month administration of SMT (n = 25) or SMT plus etilefrine (n = 25), in a randomized controlled study. A significant increase in 24-h urinary output, urinary sodium excretion, mean arterial pressure (MAP), and decrease in body weight, plasma ennin activity and plasma aldosterone concentration (P < 0.05) was noted after 1 month in the SMT/etilefrine group. Furthermore, the effective diuretic doses and the need for large-volume paracentesis were significantly reduced in the SMT/etilefrine group compared to the SMT group after 1 month of therapy. No significant changes in the aforementioned parameters were noted in the SMT group, except that MAP was significantly decreased. There was no significant change in the score of the Model for End-stage Liver Disease (MELD) in the SMT/etilefrine group; however, there was significant deterioration in the MELD score in the SMT group. These results suggest that the addition of etilefrine to SMT improves the systemic hemodynamics and enhances water and sodium excretion, providing better control in patients with refractory cirrhotic ascites treated with SMT alone.

Keywords: Etilefrine, Systemic Hemodynamics, Plasma Aldosterone Concentration, Plasma Renin Activity, Refractory Ascites, Renal Function

INTRODUCTION

Ascites is the most common of the three major complications of cirrhosis; the other complications are hepatic encephalopathy and variceal hemorrhage (Gine's et al., 1987). Approximately 50% of patients with "compensated" cirrhosis develop ascites during 10 years of observation (Gine's et al., 1987). Ascites is the most common complication of cirrhosis that leads to hospital admission (Lucena et al., 2002). Development of fluid

retention in the setting of cirrhosis is an important landmark in the natural history of chronic liver disease: approximately 15% of patients with ascites succumb in 1 year and 44% succumb in 5 years (Planas et al., 2006). Many patients are referred for liver transplantation after development of ascites. Refractory ascites develops in approximately 5 – 10 % of all cases of cirrhosis-related ascites and carries a high mortality rate (Bories et al., 1986). The available therapies for patients with refractory ascites are repeated large volume paracentesis, transjugular intrahepatic portosystemic shunts, peritoneovenous shunts, and liver transplantation (Gine's et al., 2010; Singhal et al., 2012). The mechanism by which refractory ascites develops in cirrhosis is related to splanchnic vasodilatation followed by maximal activation of the sympathetic nervous system (SNS) and the ennin – angiotensin- aldosterone system (RAAS) (Arroyo, 2002; Cardenas and Arroyo, 2003; Gine's et al., 2004; Sola and Gines, 2010). Splanchnic and peripheral vasoconstrictors (octreotide, midodrine, and terlipressin) increase effective arterial volume and decrease activation of the ennin-angiotensin system with resultant increase in renal sodium excretion (Singhal et al., 2012). Vasopressors causing splanchnic vasoconstriction have been used in hepatorenal syndrome (Moreau et al., 2002; Sanyal et al., 2008; Singh et al., 2012), for the prevention of post-paracentesis circulatory dysfunction (Singh et al., 2006; Singh et al., 2008; Appenrodt et al., 2008), improving circulatory and renal function in patients with cirrhotic ascites (Kalambokis et al., 2007; Krag et al., 2007) and for control of ascites in patients with refractory ascites (Singh et al., 2012). Combined use of midodrine with standard medical therapy (SMT) was found to improve the systemic hemodynamics without any renal or hepatic dysfunction and is superior to SMT alone for the control of refractory cirrhotic ascites (Singh et al., 2013). Clonidine, a centrally-acting presynaptic α_2 –adrenergic receptor agonist, when given with spironolactone has been shown to cause rapid mobilization of ascites by significantly decreasing the sympathetic activity and ennin-aldosterone levels (Lenaerts et al., 2006; Yang et al., 2010). Synthetic vasopressin-V_2 receptor antagonists are being evaluated for mobilization of ascites by increasing the excretion of solute-free water (Wong et al., 2003; Schrier et al., 2006; Cardenas et al., 2012). Etilefrine is a sympathomimetic agent with a potent stimulating effect on peripheral α-adrenoceptors and a mild agonist effects on β_1- and β_2- adrenoceptors. It has a potent vasoconstrictor effect. It has a stimulant effect on the cardiovascular system where it raises blood pressure to normal, improves cardiac performance and tissue perfusion. Etilefrine is indicated in hypotension and, hypotensive circulatory disorders (Effortil®- Drug information pamphlet, Boehringer Ingelheim; Drugs.com (www.drugs.com/international/effortil.html; Raviele et al., 1999). There are no published reports on the combined use of etilefrine and SMT in patients with refractory

cirrhotic ascites. Therefore, this study is designed to investigate whether the long-term use of etilefrine would improve systemic hemodynamics and control of ascites in patients with cirrhosis and refractory ascites.

METHODS

The study protocol was approved by the local ethics committee and was conducted in accordance with the principles of Helsinki declaration. Written informed consent was obtained from all patients before enrollment in the study. A total of 58 chronic hepatitis C patients with refractory cirrhotic ascites were evaluated for inclusion in the study between November 2015 and May 2016. Eight of the enrolled patients were lost during the study period for different personal unidentified reasons. Accordingly, 50 CHC patients with cirrhosis and refractory ascites with stable renal function (creatinine level < 1.5 for at least 7 days), attending Gastroenterology and Hepatology Department of a specialized hospital were prospectively included in the study. Diagnosis of cirrhosis was based on clinical, biochemical and ultrasonographic findings with or without liver biopsy (Singal and Patrick, 2013; Feldman et al., 2016). Inclusion criteria were as follows: presence of refractory ascites; patients less than 60 years of age and no treatment with drugs known to affect systemic or renal hemodynamics within one week before initiation of the study. Exclusion criteria were as follows: presence of marked hepatic encephalopathy, GIT bleeding, hepatorenal syndrome, hepatocellular carcinoma, bacterial peritonitis, portal vein thrombosis, arterial hypertension, diabetes, intrinsic renal or cardiovascular disease. Refractory ascites is defined as (a) fluid overload that is unresponsive to sodium-restricted diet and high-dose diuretic treatment (400 mg/d of spironolactone and 160 mg/d furosemide), (b) buildup of fluid that recurs rapidly after therapeutic paracentesis or (c) development of diuretic-related complications that exclude the use of an effective diuretic dosage (Singal and Patrick, 2013). Patients were randomized to either SMT alone ($n = 25$) or SMT plus oral etilefrine ($n = 25$). Etilefrine is active ingredient of Effortil® produced by Chemical Industries Development, Egypt under license of Boehringer Ingelheim International, Germany. Etilefrine was given orally at a dose of 5 mg/8h. Patients and investigators were not blinded to the treatment protocol (i.e. open-label design). SMT was defined by dietary restriction of sodium (≤ 2g/day, starting at least 7 days before the start of the study), treatment with a combination of a loop diuretic (furosemide 40-160 mg/d) and a distally-acting aldosterone antagonist (spironolactone 100-400mg/d) and repeated large volume paracentesis (LVP) along with intravenous albumin (8 g/L of ascitic fluid removed). The diuretic doses were increased by a 40/100 increment for a mean weight loss < 0.8 kg over 4 days from the previous weight. Large-

volume paracentesis was performed when ascites is tense and symptomatic. Frequency of paracentesis sessions (if any) over the 4 weeks preceding the study was obtained from patient files. All patients were subjected to baseline clinical and biochemical workup including, body weight, mean arterial blood pressure, 24-h urinary output, 24-h urinary sodium excretion, liver function tests and renal function tests. These parameters were assessed at baseline and at weekly intervals for 1 month. Measurement of mean arterial blood pressure (MAP) was calculated as diastolic blood pressure + [(systolic blood pressure - diastolic blood pressure)/3]. Three measurements were taken each 1-hour apart and the mean was calculated. Plasma renin activity and plasma aldosterone concentration were evaluated at baseline and after 1 month (endpoint). Plasma renin activity (PRA) was measured by radioimmunoassay using RIA plasma renin activity kit (Diasorin, Stillwater, MN, USA). Plasma aldosterone concentration (PAC) was measured by radioimmunoassay using ALDO-RIACT aldosterone kit (Cisbio, Parc Marcel Boiteux, France). Diuretic requirements were assessed at baseline, at weekly intervals and at endpoint. Patients were instructed to undergo tapping when become symptomatic.

Outcome measures

The primary endpoints of the study were partial or complete control of ascites. Complete response was defined as the elimination of ascites (as assessed by clinical examination and abdominal ultrasonography) ; a partial response was defined as the presence of ascites not requiring paracentesis; and absence of a response was defined as the persistence of ascites requiring paracentesis (Cardenas and Gines, 2005). Secondary endpoints include alteration of diuretic requirements, changes in the scores of end-stage liver disease, liver and renal function, and frequency of other complications of cirrhosis (e.g., encephalopathy, upper GIT hemorrhage or development of hepatorenal syndrome) after 1 month of therapy.

Statistical analysis

Data were analyzed using SPSS for MS-Windows (version 17.0, SPSS, Chicago, IL, USA). The baseline patient characteristics (clinical as well as biochemical) were compared between two groups (SMT or SMT plus etilefrine) by using Kruskal-Wallis ANOVA, Chi-square test or Fisher's exact test as appropriate. Intra-group comparisons were done using multiple repeated-measures analysis of variance. The paired t-test was performed to detect mean and standard deviation of prevalues (baseline) and postvalues (endpoint at 1 month) of the same variable of the same patients. The

results were reported as mean values ± SD. A p-value of ≤ 0.05 was taken as significant.

RESULTS

The demographic characteristics and baseline clinical and biochemical parameters were similar between SMT and SMT/etilefrine groups (Table 1). Baseline body weight did not differ significantly between the two groups ($p > 0.05$). There was a significant decrease in mean body weight in SMT/etilefrine group at 1-month as compared to baseline ($p < 0.05$) however; it did not change in the SMT group (Table 2; Figure 1).

Baseline MAP did not differ between SMT and SMT/etilefrine groups ($p > 0.05$). There was a significant increase in mean arterial pressure in SMT/etilefrine group at 1-month as compared to baseline ($p < 0.05$) and a significant decrease ($p < 0.05$) in the SMT group (Table 2; Figure 2).

Baseline urine output did not differ between SMT and etilefrine groups ($p > 0.05$). The urine output was significantly higher in the SMT/etilefrine group ($p < 0.05$) but not the SMT after 1 month of treatment as compared to baseline (Table 2; Figure 3).

Baseline urinary sodium excretion was comparable in the SMT and SMT/etilefrine groups ($p > 0.05$). Urinary sodium excretion significantly increased in the SMT/etilefrine group after treatment at 1-month as compared to baseline ($p < 0.05$); however, it did not change in the SMT group (Table 2; Figure 4).

Baseline values for plasma renin activity (Table 1) were similar in both treatment groups ($p > 0.05$). Plasma renin activity significantly decreased at 1-month ($p < 0.05$) only in the SMT/etilefrine group with no change in the SMT group compared to baseline (Table 2; Figure 5).

Baseline plasma aldosterone concentrations did not differ between the two groups ($p > 0.05$). Plasma aldosterone concentrations decreased significantly in the SMT/etilefrine group at 1-month as compared to baseline ($p < 0.05$); however, it did not change in the SMT group (Table 2; Figure 6).

Baseline values for serum creatinine in both SMT and SMT/etilefrine groups were similar ($p > 0.05$, Table 1). There was no significant change in serum creatinine in both groups after 1-month treatment as compared to baseline ($p > 0.05$, Table 2).

Baseline serum bilirubin and INR were similar in both groups ($p > 0.05$, Table 1) but there were significant increase in their values at 1 month only in the SMT group ($p < 0.05$, Table 2).

Baseline MELD score was similar in both treatment groups ($p > 0.05$; Table 1). There was a significant deterioration in MELD score in SMT group at 1 month ($p < 0.05$) with no change in the SMT/etilefrine group as compared to baseline ($p > 0.05$; Table 2).

Table 1. Baseline clinical and biochemical variables of the two study groups

Variables	SMT (n = 25; group 1)*	SMT + Etilefrine (n = 25; group 2)*
Gender		
Male (%)	23 (92)	22 (88)
Female (%)	2 (8)	3 (12)
Age (years)	48.86 ± 9.17	51.84 ± 8.95
Weight (kg)	75.82 ± 13.44	74.71 ±11.83
MAP (mmHg)	76.32 ± 6.22	74.95 ± 5.78
MELD score	12.88 ± 5.71	12.95 ± 3.89
24-h urine output (ml)	651.8 ± 263.71	670.7 ± 256.95
24-h urinary sodium excretion (mEq/l)	38.21 ± 11.72	37.62 ± 13.32
Plasma renin activity (ng/ml/h)	19.68 ± 8.88	20.72 ± 9.27
Plasma aldosterone conc. (pg/ml)	1557.8 ± 247.6	1533.7 ± 267.4
Furosemide dose (mg/day)	88.8 ± 38.5	94.3 ± 40.4
Spironolactone dose (mg/day)	237.4 ± 102.2	249.2 ± 106.6
Rate of paracentesis ≥ 5 L (times per one month)	1.14 ± 0 .79	1.18 ± 0.81
Serum bilirubin (mg/dl)	3.8 ± 1.8	4.1 ± 2.2
INR	1.71 ± 0.44	1.62 ± 0.26
Serum creatinine (mg/dl)	0.96 ± 0.25	1.10 ± 0.22

SMT, standard medical therapy, MAP, mean arterial pressure; MELD, model for end-stage liver disease; INR, international normalized ratio.
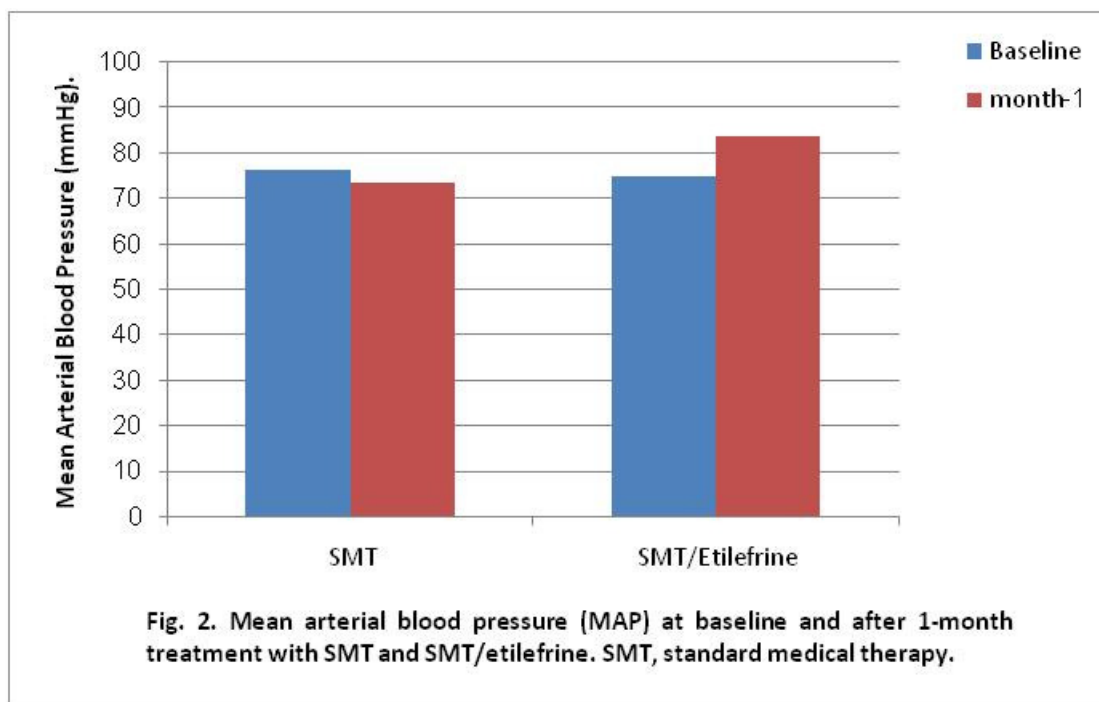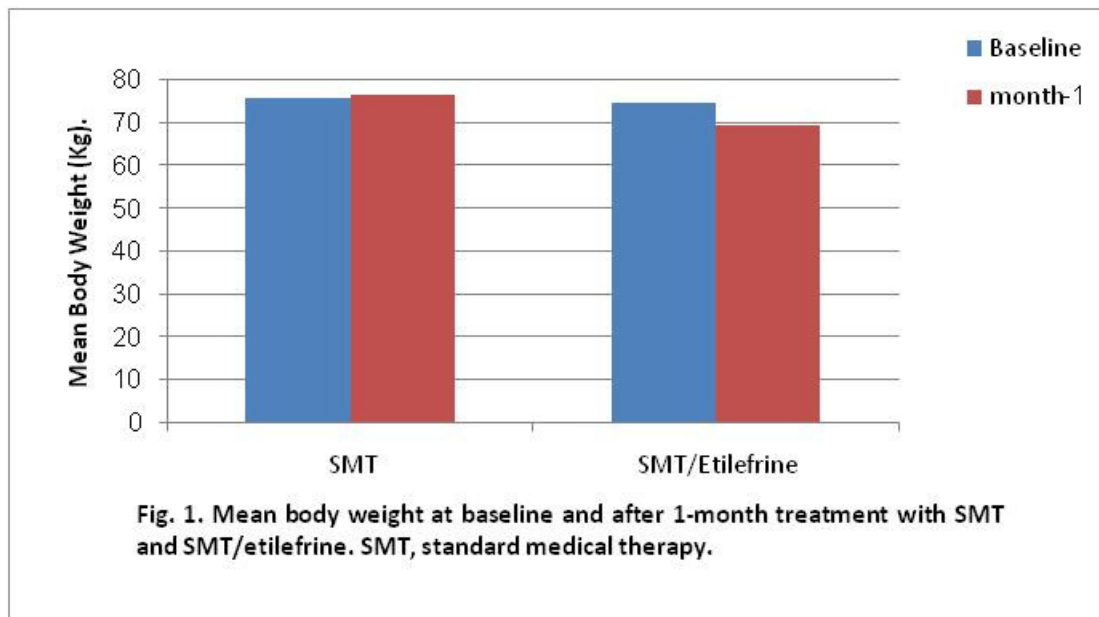*Baseline values between groups 1, and 2 are not significantly different ($P > 0.05$). Data are expressed as mean ± SD.
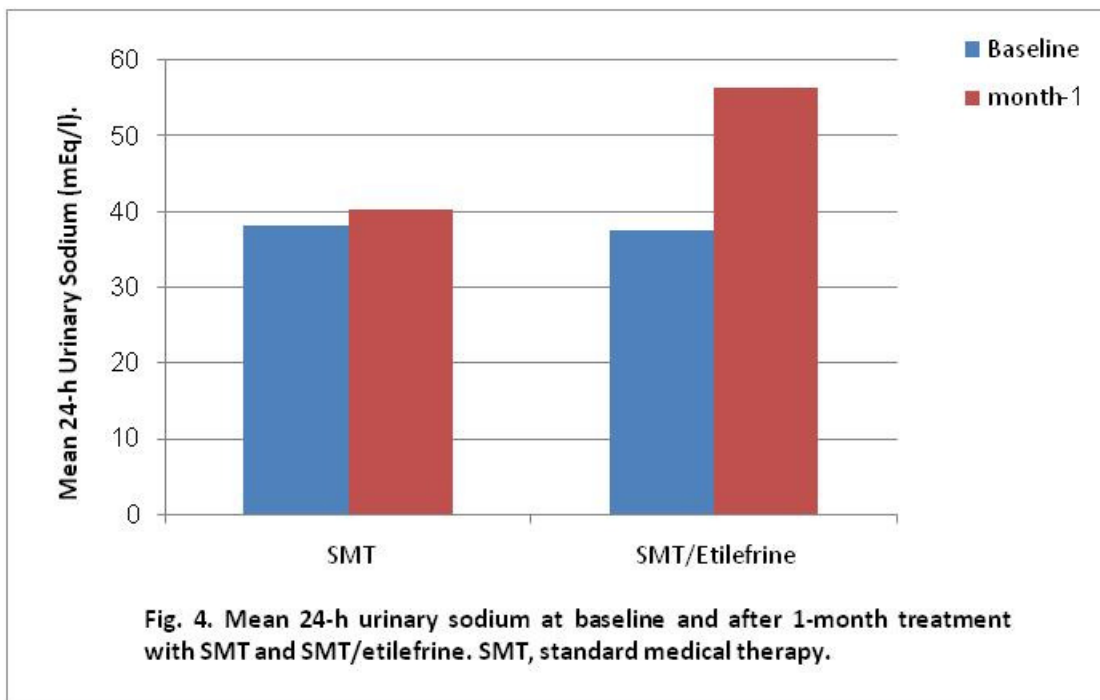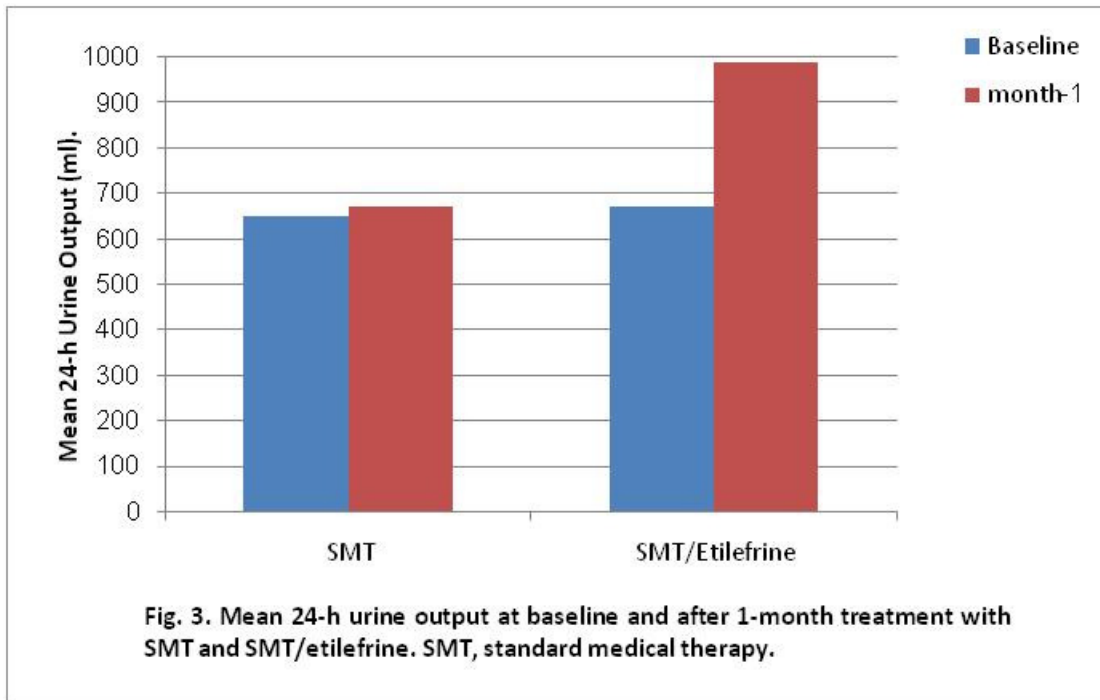
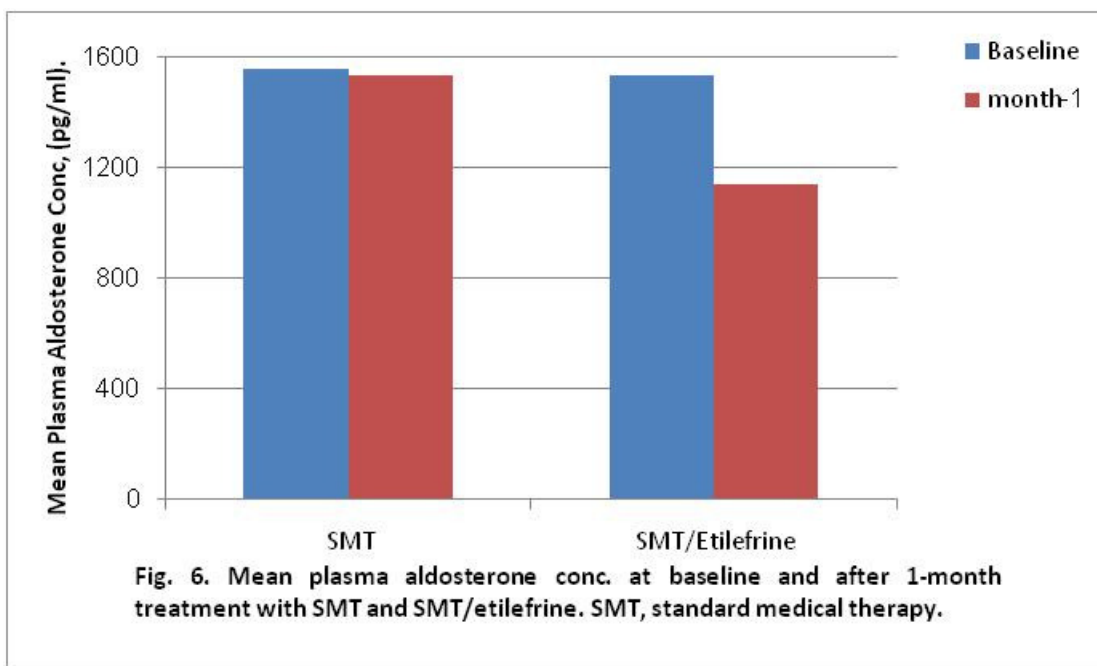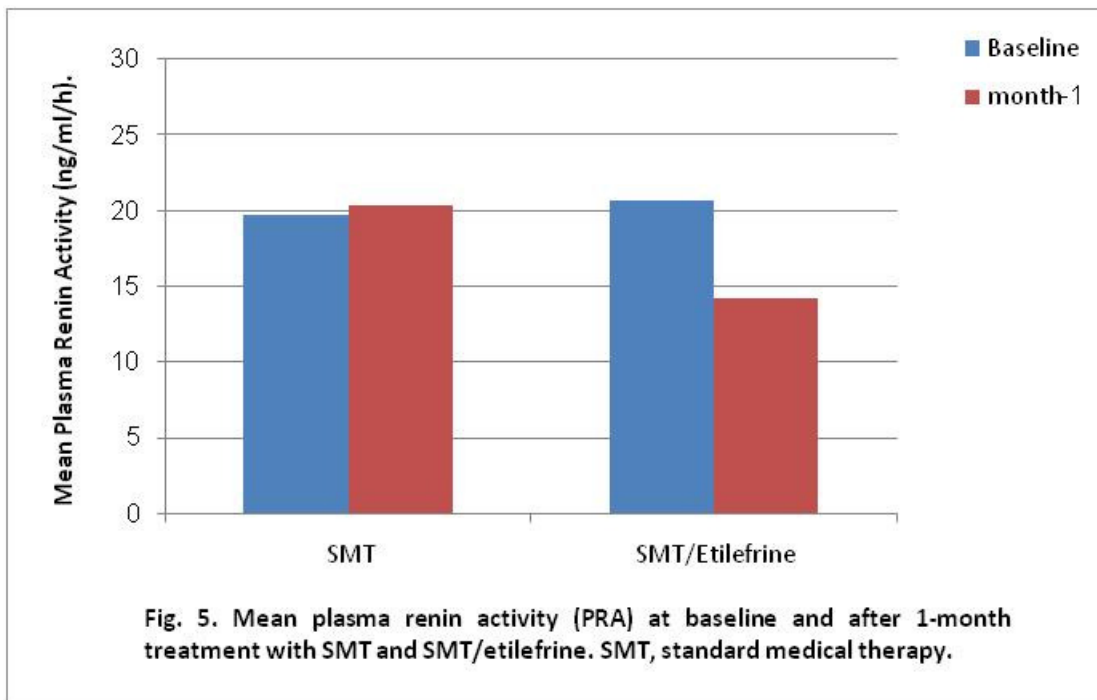**Table 2.** Clinical and biochemical parameters before and after 1 month of therapy

Variables	SMT (n = 25; group 1)		SMT + Etilefrine (n = 25; group 2)	
	Prevalues (Baseline)	Postvalues (1 Month)	Prevalues (Baseline)	Postvalues (1 Month)
Weight (kg)	75.82 ± 13.44	76.56 ± 10.61	74.71 ±11.83	69.46 ± 11.32*
MAP (mmHg)	76.32 ± 6.22	73.35 ± 5.5*	74.95 ± 5.78	83.7± 6.45*
MELD score	12.88 ± 5.71	15.90 ± 4.68*	12.95 ± 3.89	12.64 ± 4.1
24-h urine output (ml)	651.8 ± 263.71	672.3 ± 266.86	670.7 ± 256.95	988.4 ± 286.4*
24-h urinary sodium excretion (mEq/l)	38.21 ± 11.72	40.22 ± 10.58	37.62 ± 13.32	56.31± 12.2*
Plasma renin activity (ng/ml/h)	19.68 ± 8.88	20.34 ± 9.43	20.72 ± 9.27	14.21 ± 7.56*
Plasma aldosterone conc. (pg/ml)	1557.8 ± 247.6	1529.5 ± 298.2	1533.7 ± 267.4	1140.5 ± 312.6*
Serum bilirubin (mg/dl)	3.8 ± 1.8	6.7 ± 1.5*	4.1 ± 2.2	3.9 ± 1.6
INR	1.51 ± 0.42	1.7 ± 0.21*	1.56 ± 0.36	1.53± 0.28
Serum creatinine (mg/dl)	0.96 ± 0.25	0.99 ± 0.19	1.10 ± 0.22	1.00 ± 0.3
Furosemide dose (mg/day)	88.8 ± 38.5	96.0 ± 44.6	94.3 ± 40.4	48.6 ± 8.2*
Spironolactone dose (mg/day)	237.4 ± 102.2	256.0 ± 115.3	249.2 ± 106.6	98.4 ± 28.5*
Rate of paracentesis ≥ 5 L (times per one month)	1.14 ± 0 .79	1.22 ± 0.72	1.18 ± 0.81	0.6 ± 0.55*

SMT, standard medical therapy, MAP, mean arterial pressure; MELD, model for end-stage liver disease.
*1-month values are significantly different from baseline ($P < 0.05$) in the etilefrine group but not in the SMT group. Data are expressed as mean ± SD.

Fig. 1. Mean body weight at baseline and after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

Fig. 2. Mean arterial blood pressure (MAP) at baseline and after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

Fig. 3. Mean 24-h urine output at baseline and after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

Fig. 4. Mean 24-h urinary sodium at baseline and after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

Fig. 5. Mean plasma renin activity (PRA) at baseline and after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

Fig. 6. Mean plasma aldosterone conc. at baseline and after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

The need for LVP (≥ 5 L) was significantly reduced in the SMT/etilefrine group (p < 0.05; Table 2; Figure 7) at 1month compared to baseline value. No significant change was noted in the SMT group. Fifteen patients from the SMT group required LVP compared to only six in the SMT/etilefrine group over the 1-month period of therapy.

As depicted in Table 2, diuretic requirements were significantly declined from baseline in the SMT/etilefrine group (p < 0.05) with no change in the SMT group.

There was higher rate of partial response to treatment and better control of ascites in the SMT/etilefrine group (p < 0.05; Table 3; Figure 8) compared to SMT group at 1 month of treatment.

Mild abdominal pain that subsided on its own was noted in three patients in the SMT group. In the SMT/etilefrine group, mild headache was developed in
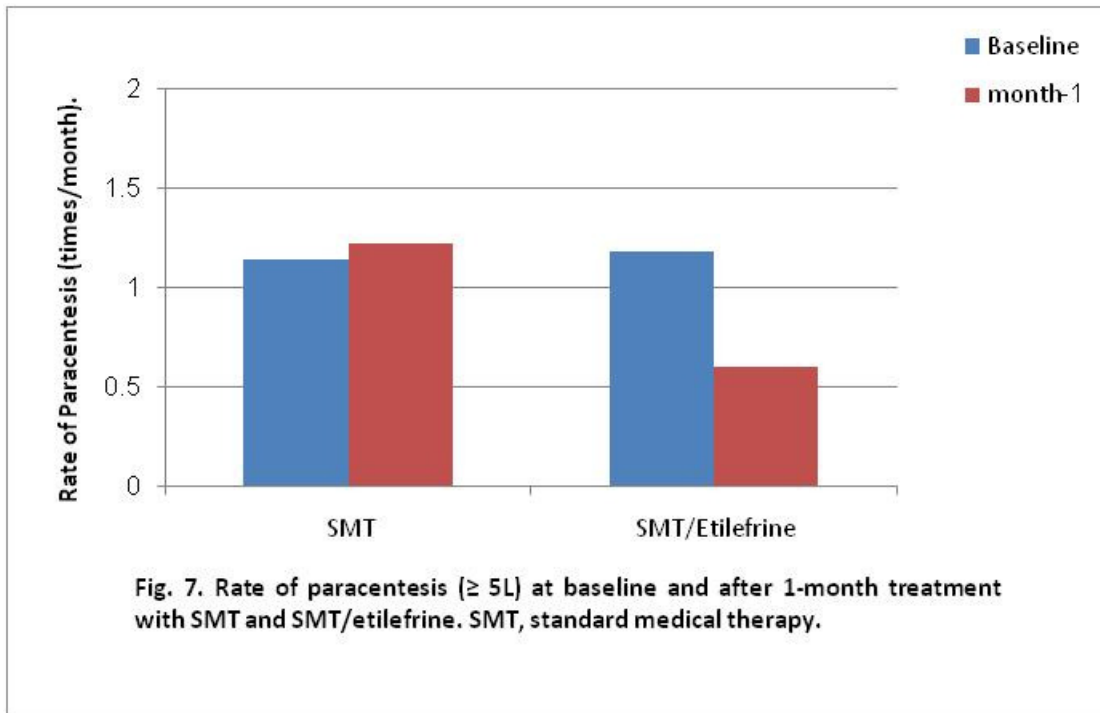
Fig. 7. Rate of paracentesis (≥ 5L) at baseline and after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

Table 3. Rates of response in study groups after 1-month (expressed as number and percentage of patients)

Response	SMT (*n* = 25; group 1)	SMT + Etilefrine (*n* = 25; group 2)
Partial	10 (40%)	19 (76%)
No response	15 (60%)	6 (24%)

SMT, standard medical therapy.

Fig. 8. Rates of resonse (%) and control of ascites after 1-month treatment with SMT and SMT/etilefrine. SMT, standard medical therapy.

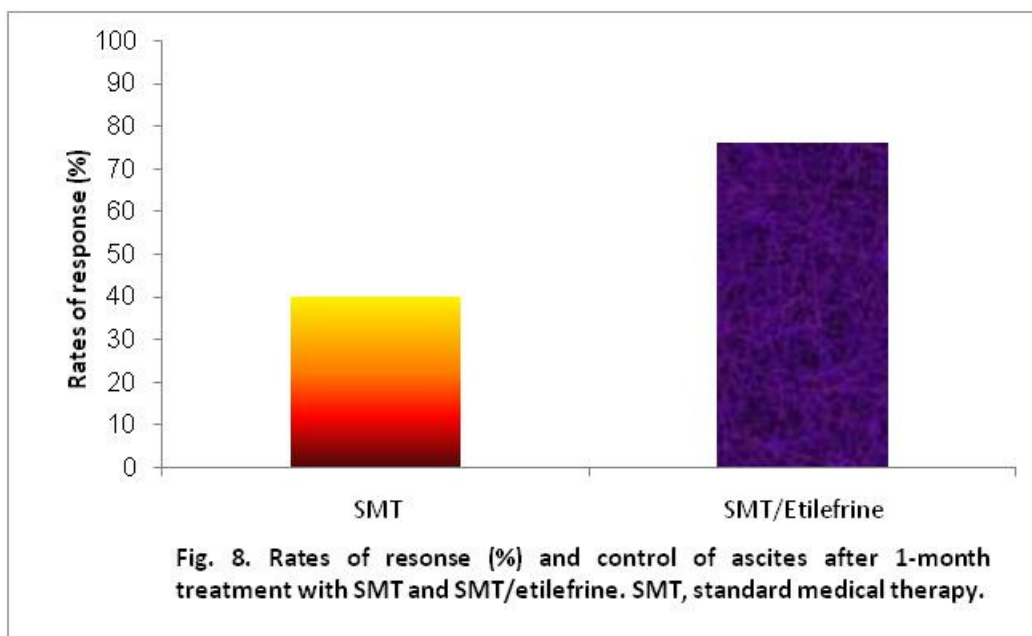**Table 4.** 1-Month morbidity and mortality in the two study groups

	SMT (*n* = 25; group 1)	SMT + Etilefrine (*n* = 25; group 2)
Death	2	0
Encephalopathy	2	0
GIT bleeding	1	0
Spontaneous bacterial peritonitis	1	1
Renal failure	1	0

two patients, which disappeared with time without discontinuation of therapy.

Follow-up

The 1-month morbidity and mortality of the study is depicted in table 4. In SMT group, encephalopathy developed in two patients, upper gastrointestinal bleeding, spontaneous bacterial peritonitis (SBP) and renal failure developed in one patient each. One case of SBP was recorded in the SMT/etilefrine group. The 1-month mortality was two in the SMT group and was related to sepsis during the follow-up period. No mortalities were recorded in the SMT/etilefrine group.

DISCUSSION

Splanchnic arterial vasodilatation induced by nitric oxide (Martin et al., 1998) and glucagons (Pizcueta et al., 1990) leads to disturbance of systemic hemodynamics reflected as reduced arterial blood pressure, reduced vascular resistance, and decreased effective blood volume with activation of potent vasoconstricting systems such as the sympathetic nervous system, the renin–angiotensin–aldosterone system, in addition to nonosmotic release of vasopressin (Arroyo and Jimenez, 2000; Schrier et al., 1988; Ferguson et al., 2006). This results in renal vasoconstriction, avid sodium and fluid retention with development of ascites (Arroyo et al., 1983). The administration of arterial vasoconstrictors has been associated with improvement in systemic hemodynamics and renal function in cirrhotic patients with ascites (Kalambokis et al., 2005). The efficacy of vasoconstrictors in advanced cirrhotic ascites might be related to failure of the activated endogenous vasopressor systems to counteract the arterial vasodilatation (Duvoux et al., 2002), probably due to reduced arterial reactivity to vasopressors (Ryan et al., 1993).

Administration of intravenous arterial vasoconstrictors such as metaraminol (Lancestremere et al., 1963), norepinephrine (Shapiro et al., 1985; Badalamenti et al., 1992), angiotensin II (Gutman et al., 1973) and terlipressin (Therapondos et al., 2004) in cirrhotic ascitic

patients has been associated with improvement of systemic hemodynamics without harmful effects on renal function.

Midodrine, a potent peripherally acting oral α-adrenergic receptor agonist, either alone (Singh et al., 2012; Singh et al., 2013; Angeli et al., 1998) or in combination with octreotide and albumin (Tandon et al., 2009) has been used to improve renal hemodynamics in cirrhotic patients with ascites. In these studies, midodrine-induced splanchnic vasoconstriction improved systemic hemodynamics with better control of ascites without any renal or hepatic dysfunction.

Combined use of midodrine with tolvaptan, an aquaretic vasopressin V_2 receptor antagonist, has been found to control ascites and improve response to diuretic therapy (Rai et al., 2016). Rai *et al.* (2016) reported that midodrine (by causing splanchnic vasoconstriction, increasing effective arterial blood volume and improving renal perfusion) and tolvaptan (by increasing free water clearance) acting at different sites in combination were more effective in combating increased renal sodium retention and refractoriness to diuretic therapy and better controlled ascites.

There are no studies in literature on the short- or long-term use of combination of etilefrine and standard medical therapy in patients with cirrhotic refractory ascites, therefore the results of the present study will be compared to previous studies in which different vasopressor agents were used for the control of refractory ascites.

In our study, we compared the changes in systemic hemodynamics (MAP), renal excretory function (24-hour urinary sodium excretion, 24-hour urinary output), plasma renin activity and plasma aldosterone concentration in patients with cirrhotic refractory ascites after 1-month treatment with SMT alone or in combination with etilefrine. Changes in models for end-stage liver disease scores, the need for paracentesis and diuretic requirements were also compared in both groups.

In the current study, there was a significant increase in the mean arterial pressure (MAP) with etilefrine while there was no change in the SMT group. Etilefrine-induced increase in MAP may be related to reducing venous pooling and counteracting reflex arteriolar vasodilatation (Raviele et al., 1999).

In agreement with our results, (Kalambokis et al., 2007; Kalambokis et al., 2005) reported an improvement in circulatory function manifested as a significant increase in MAP after short-term use of midodrine (Kalambokis et al., 2007), and chronic combined use of midodrine with octreotide (Kalambokis et al., 2005) in patients with nonazotemic cirrhotic ascites. Similar results were reported after long-term use of midodrine with SMT (Singh et al., 2012; Singh et al., 2013; Rai et al., 2016), and combined use of midodrine with SMT and clonidine (Singh et al., 2013). On contrary, Oda *et al.* (2011), reported that a 3-month course of midodrine produced no change in MAP in cirrhotic patients with refractory ascites.

In comparison to baseline values, our results showed a meaningful improvement in renal hemodynamics and function reflected as a significant increase in twenty-four-hour urine output and urinary sodium excretion in the etilefrine/SMT group but not in the SMT group. These findings agree with those observed with previous studies employing midodrine plus SMT (Singh et al., 2012; Singh et al., 2013; Rai et al., 2016), combined use of midodrine with SMT and clonidine (Singh et al., 2013), and combined use of midodrine with SMT and tolvaptan (Rai et al., 2016) In another study, a single dose of terlipressin (vasopressin V_1 receptor agonist) showed marked increase in urinary sodium excretion in patients with and without refractory ascites (Krag et al., 2007). The results of our study disagreed with a previous study (Ali et al., 2014) that found no change in 24-h urine volume after two-week midodrine therapy.

In the present study a significant decrease in plasma renin activity (PRA) and plasma aldosterone concentration was noted only in the etilefrine/SMT group after one-month therapy compared to baseline. This effect is possibly related to etilefrine-induced suppression of the renin-angiotensin-aldosterone system. Similar results with other vasoconstrictors were reported by (Singh et al., 2012; Singh et al., 2013) and (Rai et al., 2016) after long-term use of SMT/midodrine regimen (Singh et al., 2012; Singh et al., 2013; Rai et al., 2016), combined SMT/midodrine/clonidine therapy (Singh et al., 2013) or combined SMT/midodrine/tolvaptan therapy (Rai et al., 2016). In an earlier study, no change in PRA was noted in patients with refractory ascites maintained on a 3-month course of midodrine therapy (Oda et al., 2011).

In the current study, significant reduction in mean body weight was observed in patients receiving etilefrine plus SMT compared to those treated with SMT alone. This comes in concordance with previous findings of decreased body weight by midodrine (Kalambokis et al., 2005; Ali et al., 2014). The reduction in body weight may be related to a drop in fluid accumulation by etilefrine-induced vasoconstriction with reflex inactivation of the renin-angiotensin-aldosterone system (RAAS). Similar explanation were reported in previous studies in which the authors observed a significant reduction in plasma renin and aldosterone concentration and a trend toward a reduction in the volume of ascitic fluid removed by paracentesis following the administration of midodrine (Kalambokis et al., 2005; Ali et al., 2014). No change in body weight was reported in a number of previous studies utilizing different vasoconstrictors including midodrine (Singh et al., 2012; Singh et al., 2013; Rai et al., 2016).

Rate of response to treatment, measured as need for large-volume paracentesis (≥ 5L) and reduction of ascites with SMT alone or combined SMT/ etilefrine therapy was measured. There was higher rate of response to treatment, reflected as a significant decrease in the number of times of paracentesis in the combined SMT/ etilefrine therapy at 1 month. There was no significant change in rate of response to treatment in the SMT group. These results come in harmony with some previous studies in which the vasoconstrictor midodrine was used with various daily doses. [20, 48, 50] In another recent study, midodrine along with octreotide and albumin given for 1 month showed lesser requirement of paracentesis in eight patients with refractory ascites (Tandon et al., 2009).

In agreement with previous studies evaluating midodrine (Kalambokis et al., 2007; Singh et al., 2012; Singh et al., 2013; Rai et al., 2016), midodrine and clonidine (Singh et al., 2013), midodrine plus octreotide (Kalambokis et al., 2005) or midodrine plus tolvaptan (Rai et al., 2016) in cirrhotic patients with ascites, our results did not show significant change in hepatic function or MELD score in the combined SMT/etilefrine group. A significant deterioration in MELD score was noted in the SMT group at 1 month. In one recent study (Kalambokis et al., 2005), combined use of SMT with midodrine and tolvaptan showed significant improvement in MELD score at 1 and 3 month of therapy. In another pilot study, significant deterioration in the MELD score was observed during treatment with midodrine at 1 month of therapy (Tandon et al., 2009).

Diuretic needs for furosemide and spironolactone were significantly reduced in the SMT/etilefrine group at 1 month compared to baseline. Diuretic doses were reduced by increments of 40 mg (furosemide) /100 mg (spironolactone) for each ≥ 0.8 kg mean decrease in body weight from the previous weight over 4 days of therapy according to the criteria of International Ascites Club (Moore et al., 2003).

The reduction of diuretic requirements and subsequent enhancement in diuretic response may be related to etilefrine-induced improvement in renal perfusion and/or its inhibitory effect on RAAS. No significant change in diuretic needs was noted in patients receiving SMT alone. Reduction in diuretic needs with better control of ascites was reported in one earlier pilot study (Singh et al., 2013).

There was higher rate of partial response to treatment (defined as ascites requiring no paracentesis) and better

control of ascites in the SMT/etilefrine group compared to SMT group at 1 month of treatment (76 versus 40%, p < 0.05; Table 3).

Etilefrine use was well tolerated by the majority of patients. Only two patients developed mild headache that resolved spontaneously within few days without discontinuation of treatment.

CONCLUSION

To our knowledge, this is the first study of long-term use of combined SMT/etilefrine therapy in patients with cirrhotic refractory ascites. In patients receiving combined SMT/etilefrine therapy, we observed a significant increase in MAP, 24-h urinary output, 24-h urinary sodium excretion and a significant reduction in body weight, plasma renin activity and aldosterone concentration. There was a considerable reduction in the need for large volume paracentesis and diuretic therapy. Large multicentre, randomized-controlled trials are required before combined SMT/etilefrine therapy can be routinely recommended.

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Conflict of Interest

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