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HALPHABAROL THERAPY IN EGYPTIAN PATIENTS WITH CIRRHOSIS AND DIURETIC-RESISTANT ASCITES

Ahmed M. Ali*[1], BSc. Pharm, PhD and Kamal A. Ramzy[2], MD, MMed

[1]*Department of Clinical Pharmacy, Faculty of Pharmacy, October 6 University, October 6 City, Central Axis, Part 1/1, Giza, Egypt.
[2]General Authority of Teaching Hospitals, Cairo, Egypt.

***Corresponding Author: Dr. Ahmed M. Ali**
Department of Clinical Pharmacy, Faculty of Pharmacy, October 6 University, October 6 City, Central Axis, Part 1/1, Giza, Egypt.

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ABSTRACT

Background: Liver cirrhosis accounts for over 75% of all episodes of ascites. 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 diuretic therapy. Diuretic–resistant ascites is defined as failure to respond to maximal tolerated doses of spironolactone and frusemide. At this point, the need for serial therapeutic paracentesis (abdominal tapping) becomes a must. **Objectives:** The aim of this study is to evaluate the diuretic effects of halphabarol and its possible role in the mobilization and control of ascites in cirrhotic ascitic patients resistant to maximal tolerated doses of standard diuretic therapy (SDT). **Patients and methods:** A total of 44 cirrhotic patients with diuretic-resistant ascites were prospectively studied after 1 month administration of SDT alone ($n = 22$) or in combination with halphabarol ($n = 23$) in a randomized controlled open-label pilot study. **Results:** Significant increases in 24-h urinary output, urinary sodium excretion, random urinary sodium/potassium ratio and significant reductions in body weight, abdominal girth, plasma renin activity and plasma aldosterone concentration ($P < 0.05$) were noted after 1 month in the halphabarol group. Furthermore, the effective diuretic doses and the need for large-volume paracentesis were significantly reduced in the halphabarol group compared to the SDT group after 1 month of therapy. No significant changes in the aforementioned parameters were noted in the SDT group. There were no significant changes in the scores of end-stage liver disease in both groups. **Conclusions:** These results suggest that the addition of halphabarol to SDT improves enhances water and sodium excretion, providing better control in cirrhotic ascitic patients resistant to SDT.

KEYWORDS: Diuretic-resistant ascites, halphabarol, plasma renin activity, plasma aldosterone concentration, abdominal girth.

INTRODUCTION

Ascites is one of the most common complications of liver cirrhosis.[1] Liver cirrhosis-associated ascites can be controlled in about 90% of patients using oral diuretics (usually spironolactone and furosemide) and dietary sodium restriction.[2]

Diuretic-resistant ascites is considered to develop in patients with cirrhosis when one or both of the following criteria is present: (a) An inability to mobilize ascites despite compliance with dietary sodium restriction and the administration of maximum tolerable doses of oral diuretics and/or (b) The development of diuretic-related complications, such as hepatic encephalopathy, renal impairment, or progressive electrolyte imbalance including hyponatremia and hypo- or hyperkalemia.[3-6]

Diuretic-resistant ascites is usually associated with advanced cirrhosis, marked activation of the sympathetic nervous system and renin-angiotensin-aldosterone system and very low urinary sodium excretion despite maximal tolerated doses of diuretics.[2,4] Activation of the aforementioned systems results in renal vasoconstriction and enhanced sodium reabsorption in the proximal tubule (under the influence of noradrenaline and angiotensin-2) and collecting tubules (under the influence of aldosterone). Cirrhotic patients with a greater degree of sympathetic nervous system and renin-angiotensin system stimulation usually show diminished diuretic responsiveness.[7,8] The development of diuretic resistance in a previously diuretic-sensitive patient is most often due to progression of liver disease or occurrence of other complications of cirrhosis, namely hepatocellular carcinoma (HCC) and/or portal vein thrombosis.[9]

The 2-year survival rate of all patients with cirrhosis after the development of ascites is approximately 50%[10,

11], compared to 50% at 6-months and 25 % at 1-year in patients with diuretic-resistant ascites.[12] Ascitic patients with baseline urinary sodium excretion < 10 mEq/day had a mean survival rate of 5-6 months compared to over 2-years in those with ascites and a higher rate of sodium excretion.[13] The three major therapeutic options available for patients with refractory ascites are serial therapeutic paracentesis, liver transplantation and transjugular intrahepatic portosystemic stent shunt.[14, 15]

The ideal treatment of ascites should be effective in mobilization of ascites and prevention of recurrence, should improves patient's quality of life and survival and should be acting directly on one or more steps in the pathogenesis of ascites and not just the mechanical removal of the fluid.[16]

Liver transplantation is the only definitive therapeutic option for refractory ascites; however, the management of ascites is an important issue until transplantation becomes available and in those who are not transplant candidates.[6]

Halfa-Bar (*Cymbopogon proximus*), is an aromatic wild grass widely growing in Upper Egypt, its genus *Cymbopogon*, belongs to family Gramineae.[17,18] The plant is used extensively in folk medicine against fever, influenza, neurotic disorders, as antihypertensive, antirheumatic, carminative, stomachic and sudorific.[19] This herb is also recommended for medical purposes as an effective diuretic, renal or abdominal antispasmodic agent[20], expulsion of renal and ureteric calculi[21] anti-hyperglycemic[22] and protection against allaxon-induced liver and renal damage in rats.[22] Terpenes, tannins, flavonoids, saponins, alkaloids, carbohydrate or glycosides, and phenolic glycosides are the phytochemical compositions which are found in the aqueous extract of *C. Proximus*.[23-26] Due to its efficiency as a diuretic and a renal antispasmodic agent and for the expulsion of ureteric calculi, the medicinal product PROXIMOL (Halphabarol) was manufactured by Kahira Pharmaceutical Company, Cairo, Egypt (Ministry of Health, Egypt, product registration #24526) which depends completely on plant material collected from the wild weed.[27]

The primary objective of the study is to show if combined SDT/halphabarol therapy is superior to SDT alone in the control of diuretic-resistant ascites.

METHODS

The study protocol was approved by the local ethics committee and was conducted in accordance with the principles of Helsinki declaration.[28] Written informed consent was obtained from all patients before enrollment in the study.

A total of 51 chronic hepatitis C patients with cirrhotic diuretic-resistant ascites were evaluated for inclusion in the study between August 2015 and October 2016. Six of the enrolled patients were dropped during the study period for different reasons (encephalopathy in 3, variceal bleeding in 1 and death in 2 patients). Accordingly, 45 patients with cirrhosis and diuretic-resistant 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.[29, 30] Diuretic-resistant ascites were defined according to the criteria of International Ascites Club.[31]

Inclusion criteria were as follows: presence of diuretic-resistant ascites; patients less than 60 years of age; no previous paracentesis 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.

In this study, standard diuretic therapy (SDT) was defined by dietary restriction of sodium (≤ 2g/day, starting at least 7 days before the start of the study) and treatment with a combination of a loop diuretic (furosemide 40-160 mg/d) and a distally-acting aldosterone antagonist (spironolactone 100-400mg/d) for at least 1 week before the study. 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.

Patients were randomized to either SDT alone (n = 22) or SDT plus oral halphabarol (n = 23) (Proximol, 0.4 mg tablets) at a dose of 0.8 mg (two 0.4 mg tablets) given 8-hourly for 1 month. Patients and investigators were not blinded to the treatment protocol (i.e. open-label design).

All patients were subjected to baseline clinical and biochemical workup including, body weight, abdominal girth measurements, 24-h urinary output, 24-h urinary sodium excretion, random urinary Na/K ratio, liver function tests and renal function tests. These parameters were assessed at baseline and at weekly intervals for 1 month. 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 was measured by radioimmunoassay using ALDO-RIACT aldosterone kit (Cisbio, Parc Marcel Boiteux, France). Abdominal girth was measured by taking the average of three readings; one at the level of the umbilicus, one just above and one

just below the umbilicus. Random urine samples were obtained after completion of 24-hour urine collection for measurement of spot Na and K concentrations to calculate their ratios (UNa/K ratios). Diuretic requirements were assessed at baseline, at weekly intervals and at endpoint. Percentage of patients requiring paracentesis was determined over the 1-month period of the study in both groups.

The compliance of patients to study medication was assessed at each office visit (2 visits weekly) through leading questions and by counting the number of tablets removed from medication pack. In addition, follow-up telephone calls were performed when necessary. The study medication "Proximol" was supplied freely to all patients.

Drug Used

Halphabarol, the active principle of "PROXIMOL" is one of the most potent constituents present in the national desert weed "*Cymbopogen proximus*" or "Halfa-Bar". Tablets of Proximol were obtained from Kahira Pharmaceutical Company, Cairo, Egypt. The concentration of active ingredient in each tablet is 0.4 mg Halphabarol. Proximol was administrated orally in a dose of 0.8 mg (2 tablets) 8-hourly for one month.

Outcome measures

The primary objective was to show if combined SDT/halphabarol therapy is superior to SDT alone with respect to mean fall in body weight, abdominal girth, plasma renin activity, plasma aldosterone concentration and mean increase in 24-hour urinary output, 24-hour urinary sodium excretion and random UNa/K ratio from baseline at the end of 1-month therapy. One of the primary outcome measures is to demonstrate which of the two regimens can achieve better control of ascites. Complete control was defined as the elimination of ascites (as assessed by clinical examination and abdominal ultrasonography); a partial control was defined as the presence of ascites not requiring paracentesis; and absence of a control was defined as the persistence of ascites requiring paracentesis Secondary endpoints include reduction of diuretic requirements, changes in the rate of paracentesis and scores of the model for end-stage liver disease (MELD) and morbidity and mortality rates 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 (SDT or SDT plus halphabarol) 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 SDT and SMT/halphabarol groups (Table 1).

Baseline body weight and abdominal girth did not differ significantly between the two groups ($p > 0.05$). There was a significant decrease in mean body weight and abdominal girth in SDT/halphabarol group at 1-month as compared to baseline ($p < 0.05$) however; it did not change in the SDT group (Table 2; Figs. 1& 2).

Baseline 24-hour urine output did not differ between SDT and halphabarol groups ($p > 0.05$). The urine output was significantly higher in the SDT/ halphabarol group ($p < 0.05$) but not the SDT after 1 month of treatment as compared to baseline (Table 2; Fig. 3).

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

Baseline random urinary sodium/potassium ratio is shown in Table 1. Random urinary sodium/potassium ratio was significantly increased in the SDT/ halphabarol group after treatment at 1-month as compared to baseline ($p < 0.05$); however, it did not change in the SDT group (Table 2; Fig. 5).

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 SDT/halphabarol group with no change in the SDT group compared to baseline (Table 2; Fig. 6).

Baseline plasma aldosterone concentrations did not differ between the two groups ($p > 0.05$). Plasma aldosterone concentrations decreased significantly in the SDT/ halphabarol group at 1-month as compared to baseline ($p < 0.05$); however, it did not change in the SDT group (Table 2; Fig. 7).

Baseline values for serum creatinine, serum bilirubin and INR in both SDT and SDT/halphabarol groups were similar ($p > 0.05$, Table 1). There were no significant changes in those parameters in both groups after 1-month treatment as compared to baseline ($p > 0.05$, Table 2).

Baseline MELD score was similar in both treatment groups ($p > 0.05$; Table 1). There was no significant deterioration in MELD score in both groups at 1 month ($p > 0.05$; Table 2).

The need for LVP (≥ 5 L) was significantly reduced in the SDT/halphabarol group ($p < 0.05$; Table 2; Fig. 8) at 1month compared to baseline value. No significant change was noted in the SDT group.

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

There was higher rate of partial control (ascites not requiring paracentesis) of ascites in the SDT/halphabarol group compared to SDT group at 1 month of treatment. Fourteen patients from the SDT group required LVP compared to only seven in the SDT/halphabarol group over the 1-month period of therapy ($p < 0.05$; Table 3; Fig. 9).

Mild abdominal pain that subsided on its own was noted in three patients in the SDT group. In the SDT/ halphabarol group, mild headache was developed in 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 SDT group, encephalopathy, upper gastrointestinal bleeding and spontaneous bacterial peritonitis (SBP) developed in one patient each. One case of SBP was recorded in the SDT/ halphabarol group. The 1-month mortality was one in the SDT group and was related to sepsis during the follow-up period. No mortalities were recorded in the SDT/halphabarol group.

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

Variables	SDT (*n* = 22; group 1)*	SDT + Halphabarol (*n* = 23; group 2)*
Gender		
Male (%)	20 (90.9)	20 (86.9)
Female (%)	2 (9.1)	3 (13.1)
Age (years)	47.76 ± 9.18	49.23 ± 8.89
Weight (kg)	76.85 ± 12.45	75.92 ±12.73
Abdominal girth (Cm)	102.70	103.15
MELD score	12.75 ± 5.73	12.81 ± 3.78
24-h urine output (ml)	645.6 ± 268.81	656.7 ± 254.95
24-h urinary sodium excretion (mEq/l)	39.31 ± 10.68	38.98 ± 12.44
24-h urinary potassium excretion (mEq/l)	41.23 ± 14.51	40.12 ± 13.61
Random urinary Na/K ratio	0.95	0.97
Plasma renin activity (ng/ml/h)	20.68 ± 9.88	20.70 ± 8.37
Plasma aldosterone conc. (pg/ml)	1547.8 ± 247.6	1535.7 ± 267.4
Furosemide dose (mg/day)	90.8 ± 36.5	91.1 ± 32.5
Spironolactone dose (mg/day)	240.6 ± 98.3	243.2 ± 90.7
Rate of paracentesis ≥ 5 L (times per one month)	2.20 ± 0 .88	2.35 ± 0.77
Serum bilirubin (mg/dl)	3.9 ± 1.7	4.2 ± 2.1
INR	1.49 ± 0.39	1.51 ± 0.34
Serum creatinine (mg/dl)	0.93 ± 0.22	0.94 ± 0.25

SDT, standard diuretic therapy; 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	**SDT (*n* = 22; group 1)**		**SDT + Halphabarol (*n* = 23; group 2)**	
	Prevalues (Baseline)	**Postvalues (1 Month)**	**Prevalues (Baseline)**	**Postvalues (1 Month)**
Weight (kg)	76.85 ± 12.45	77.28 ± 11.51	75.92 ±12.73	68.76 ± 10.92*
Abdominal girth (Cm)	102.70	100.55	103.15	97.25*
MELD score	12.75 ± 5.73	12.92 ± 4.68	12.81 ± 3.78	12.65 ± 4.1
24-h urine output (ml)	645.6 ± 268.81	640.7 ± 265.56	656.7 ± 254.95	975.7 ± 296.8*
24-h urinary sodium excretion (mEq/l)	39.31 ± 10.68	38.73 ± 11.28	38.98 ± 12.44	54.42 ± 11.5*
24-h urinary potassium excretion (mEq/l)	41.23 ± 14.51	41.85 ± 16.31	40.12 ± 13.61	37.55 ± 10.36
Random urinary Na/K ratio	0.95	0.92	0.97	1.45*
Plasma renin activity (ng/ml/h)	20.68 ± 9.88	20.28 ± 8.43	20.70 ± 8.37	13.32 ± 7.46*
Plasma aldosterone conc. (pg/ml)	1547.8 ± 247.6	1538.5 ± 298.2	1535.7 ± 267.4	1138.5 ± 312.6*
Serum bilirubin (mg/dl)	3.9 ± 1.7	4.1 ± 1.6	4.2 ± 2.1	4.0 ± 1.5
INR	1.49 ± 0.39	1.46 ± 0.23	1.51 ± 0.34	1.50 ± 0.27
Serum creatinine (mg/dl)	0.93 ± 0.22	0.95 ± 0.17	0.94 ± 0.25	0.92 ± 0.43
Furosemide dose (mg/day)	90.8 ± 36.5	95.0 ± 48.4	91.1 ± 32.5	45.5 ± 7.4*
Spironolactone dose (mg/day)	240.6 ± 98.3	258.0 ± 92.4	243.2 ± 90.7	100.6 ± 36.7*
Rate of paracentesis ≥ 5 L (times per one month)	2.20 ± 0 .88	2.6 ± 0.78	2.35 ± 0.77	0.8 ± 0.58*
SDT, standard diuretic therapy; MELD, model for end-stage liver disease; INR, international normalized ratio. *1-month values are significantly different from baseline ($P < 0.05$) in the SDT/Halphabarol group but not in the SDT group. Data are expressed as mean ± SD.				

Table 3. Rates of ascites control in study groups after 1-month (expressed as number and percentage of patients)		
Response	**SDT (*n* = 22; group 1)**	**SDT + Halphabarol (*n* = 23; group 2)**
Partial	8 (36.4%)	16 (69.6%)*
No response	14 (63.6%)	7 (30.4%)*
SDT, standard diuretic therapy. *Significantly different from SMT group ($P < 0.05$)		

Table 4. Morbidity and mortality in the two study groups		
	SDT (*n* = 22; group 1)	**SDT + Halphabarol (*n* = 23; group 2)**
Death	1	0
Encephalopathy	1	0
GIT bleeding	1	0
Spontaneous bacterial peritonitis	1	1

FIGURES

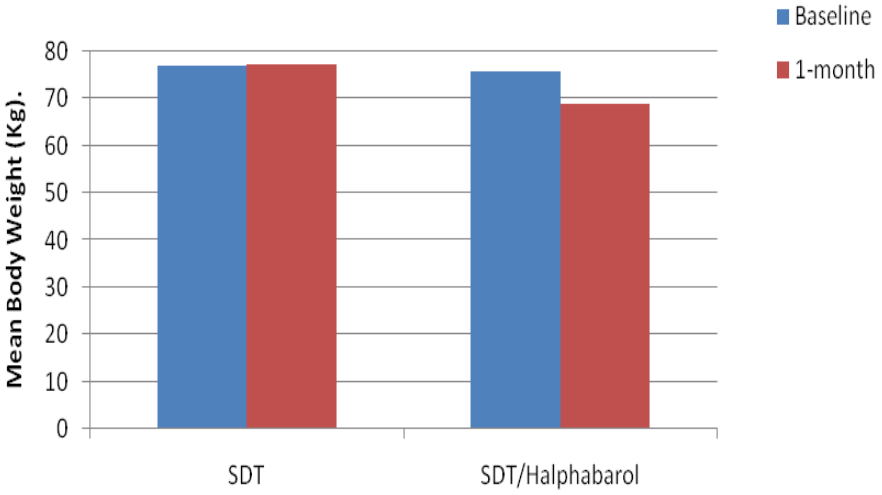

Fig. 1. Mean body weight at baseline and after 1-month treatment with SMT and SDT/Hlphabarol. SDT, standard diuretic therapy.

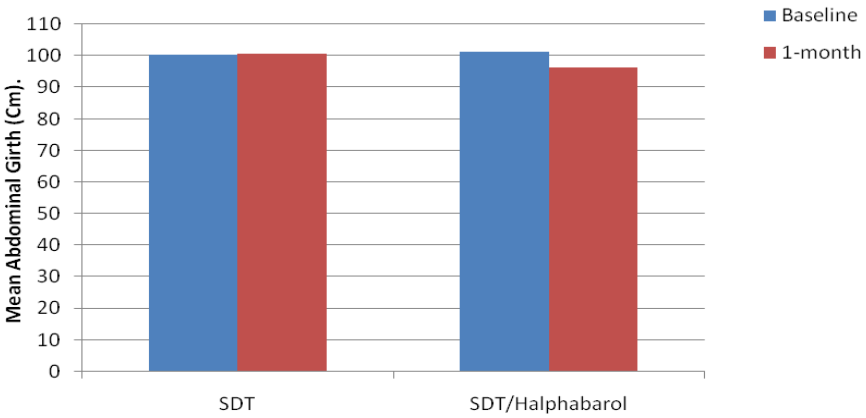

Fig. 2. Mean abdominal girth at baseline and after 1-month treatment with SDT and SDT/Halphabarol. SDT, standard diuretic therapy.

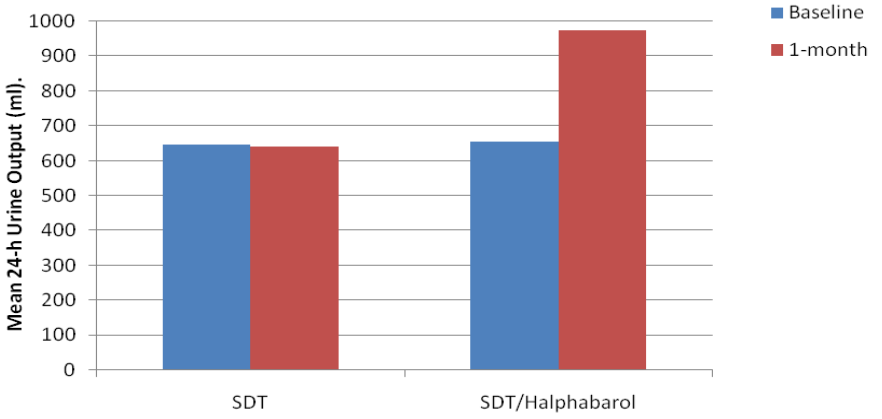

Fig. 3. Mean 24-h urine output at baseline and after 1-month treatment with SDT and SDT/Halphabarol. SDT, standard diuretic therapy.

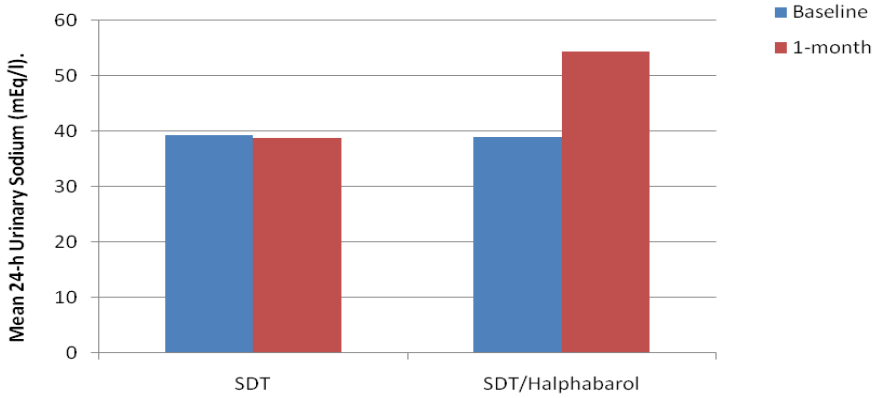

Fig. 4. Mean 24-h urinary sodium at baseline and after 1-month treatment with SDT and SDT/Hlphabarol. SDT, standard diuretic therapy.

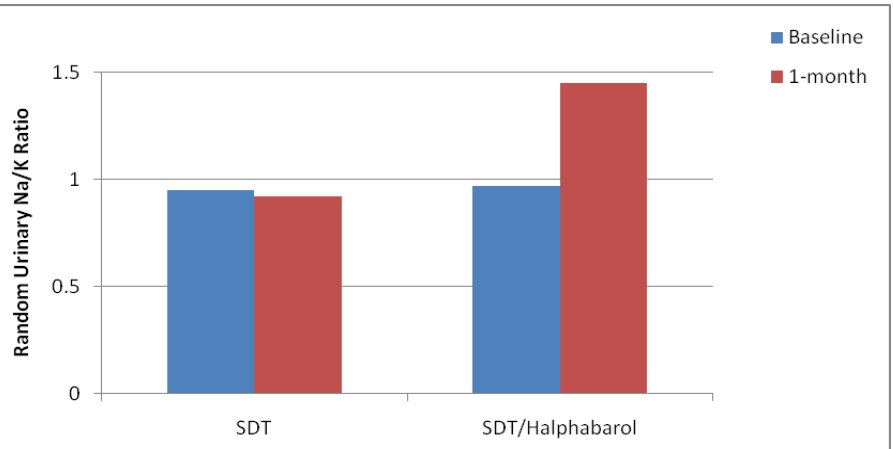

Fig. 5. Random urinary sodium/potassium ratio at baseline and after 1-month treatment with SDT and SDT/Halphbarol. SDT, standard diureticl therapy.

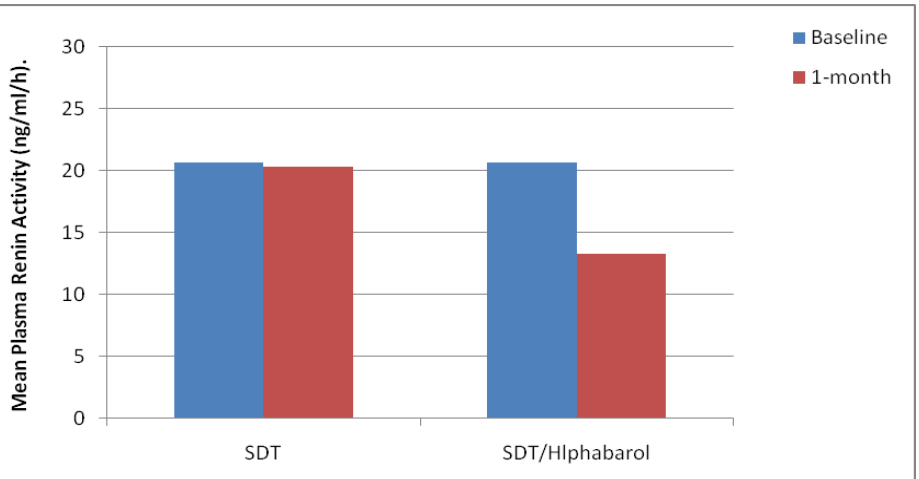

Fig. 6. Mean plasma renin activity (PRA) at baseline and after 1-month treatment with SDT and SDT/Halphabarol. SDT, standard diuretic therapy.

Fig. 7. Mean plasma aldosterone conc. at baseline and after 1-month treatment with SDT and SDT/Halphabarol. SDT, standard diuretic therapy.

Fig. 8. Rate of paracentesis (≥ 5L) at baseline and after 1-month treatment with SDT and SDT/Halphabarol. SDT, standard diureticl therapy.

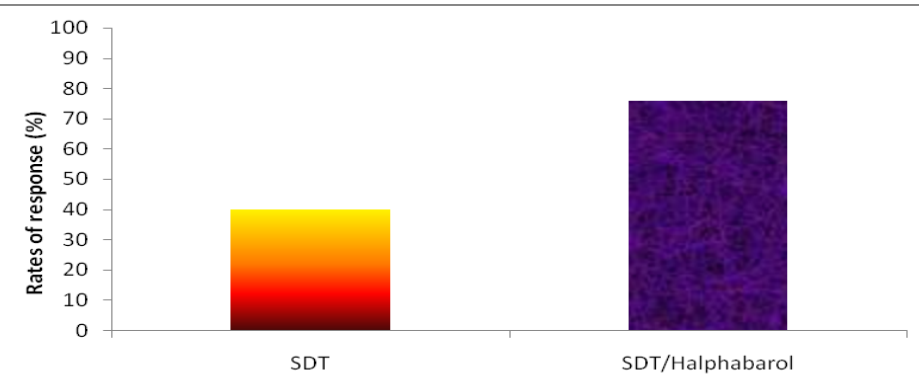

Fig. 9. Rates of resonse (%) and control of ascites after 1-month treatment with SDT and SDT/Halphabarol. SDT, standard diuretic therapy.

DISCUSSION

Ascites is the most common of the major complications of cirrhosis. With disease progression, patients with advanced cirrhosis and severe urinary sodium retention develop refractory ascites, a condition in which patients do not respond to diuretics or develop severe side effects to them that exclude their use. This condition occurs in 5–10% of cases admitted to the hospital for treatment of ascites. Approximately half of these patients will die within 1 year if not transplanted.[1, 14, 32]

One of the key events thought to be critical in the pathogenesis of cirrhotic ascites formation and sodium retention is the development of systemic vasodilatation, which causes a decrease in effective arterial blood volume and a hyperdynamic circulation.[33] The mechanism responsible for these changes in vascular function may involve increased vascular synthesis of nitric oxide, prostacyclin, as well as changes in plasma concentrations of glucagon, substance P, or calcitonin gene related peptide.[34]

The development of renal vasoconstriction in cirrhosis may be related to increased renal sympathetic activity and activation of the renin-angiotensin system to maintain blood pressure during systemic vasodilatation.[35] Decreased renal blood flow decreases glomerular filtration rate and thus the delivery and fractional excretion of sodium. Cirrhosis is associated with enhanced reabsorption of sodium both at the proximal tubule and at the distal tubule. Increased reabsorption of sodium in the distal tubule is due to increased circulating concentrations of aldosterone.[35]

There are no studies in literature on the short- or long-term use of combination of halphabarol and standard diuretic therapy in patients with cirrhotic diuretic-resistant ascites, therefore the results of the present study will be compared to previous studies in which different therapeutic regimens were used for the control of refractory ascites. Halphabarol is widely used as an effective diuretic and smooth muscle relaxant in both folklore and modern medicine.[18, 27]

In our study, we compared the changes in body weight, abdominal girth, 24-hour urinary output, 24-hour urinary sodium excretion, random urinary Na/K ratio, plasma renin activity and plasma aldosterone concentration in patients with cirrhotic refractory ascites after 1-month treatment with SDT alone or in combination with halphabarol. Changes in the model for end-stage liver disease (MELD) score, the need for paracentesis and diuretic requirements were also compared in both groups.

In the current study, there were significant decreases in the mean body weight and abdominal girth with halphabarol group with no change in the SDT group. Halphabarol-induced reduction in body weight and abdominal girth may be related to improved urinary output and mobilization of peritoneal fluid. A reduction in body weight[36] and abdominal girth[37] were previously reported in patients with non-azotemic cirrhotic ascites receiving a combination of midodrine and standard diuretic therapy.

In comparison to baseline values, our results showed a significant increase in twenty-four-hour urine output and urinary sodium excretion and random urinary Na/K ratio in the Halphabarol/SDT group but not in the SDT group. Similar findings were observed with previous studies employing midodrine plus SDT[38, 39, 40], combined use of midodrine with SDT and clonidine[38] and combined use of midodrine with SDT and tolvaptan.[40] 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.[41] According one study[37], no change in 24-h urine volume was observed after two-week midodrine therapy.

The random urine Na/K ratio is one of the useful tools for predicting therapeutic response for diuretics in cirrhotic patients with ascites.[42] Also in patients with decompensated cirrhosis and ascites, a ratio of sodium to potassium of less than one in randomly collected urine samples was associated with renal dysfunction and short-term mortality.[43] In our study, diuretic-resistant ascitic patients receiving combined halphabarol/SDT showed a change in random urinary Na/K ratio from less than one at baseline to more than one at endpoint.

In the present study a significant decrease in plasma renin activity (PRA) and plasma aldosterone concentration was noted only in the halphabarol/SDT group after one-month therapy compared to baseline. This effect is probably related to halphabarol-induced suppression of the renin-angiotensin-aldosterone system. Similar results were reported reported by Singh *et al.*,[19,20] and Rai *et al.*,[40] after long-term use of midodrine with SDT[38,39,40], combined SDT/midodrine/clonidine therapy[39] or combined SDT/midodrine/tolvaptan therapy.[40] In an earlier study, no change in PRA was noted in patients with refractory ascites maintained on a 3-month course of midodrine therapy.[44]

The rate of response to treatment and ascites control, measured as need for large-volume paracentesis (≥ 5L) with SDT alone or combined SDT/halphabarol 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 SDT/halphabarol therapy at 1 month. There was no significant change in rate of response to treatment in the SDT group. These results are similar to those of some previous studies in which different doses of midodrine were used in combination with SDT.[37, 39, 40] 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.[45]

The improvement in ascites control may be partly related to halphabarol-mediated enhanced diuresis. Also, since free radical production and oxidative stress are known to play a role in the pathogenesis of hepatic cirrhosis[46, 47] and viral hepatitis[48], halphabarol's antioxidant activity[49, 50] may be of value in ascites control probably through neutralizing free radicals, quenching singlet and triplet oxygen and/or decomposing peroxides.

Our results did not show significant change in hepatic function or MELD score in both treatment arms as compared to baseline values.

Diuretic needs for furosemide and spironolactone were significantly reduced in the SDT/halphabarol group at 1 month compared to baseline. The reduction of diuretic requirements and subsequent enhancement in diuretic response may be related to halphabarol-induced improvement in renal perfusion and/or its inhibitory effect on RAAS. No significant change in diuretic needs was noted in patients receiving SDT alone.

There was higher rate of partial control of ascites in the SDT/halphabarol group compared to SDT group at 1 month of treatment (69.6% versus 36.4% respectively).

Halphabarol therapy was well tolerated by patients.Only mild headache was developed in two patients, which disappeared with time without discontinuation of therapy.

CONCLUSION

To our knowledge, this is the first study of long-term use of combined SDT/halphabarol therapy in patients with cirrhotic diuretic-resistant ascites. In patients receiving combined SDT/ halphabarol therapy, we observed a significant increase in 24-h urinary output, urinary sodium excretion, random urinary sodium/potassium ratio and significant reductions in body weight, abdominal girth, plasma renin activity and plasma aldosterone concentration. The effective diuretic doses and the need for large-volume paracentesis were significantly reduced in the halphabarol group compared to the SDT group after 1 month of therapy. No significant changes in the aforementioned parameters were noted in the SDT group.We conclude that the addition of halphabarol to SDT improves enhances water and sodium excretion, providing better control in cirrhotic ascitic patients resistant to SDT. Large multicentre, randomized-controlled trials are required before combined SDT/halphabarol therapy can be routinely recommended.

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Conflict of interest

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