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Intravenous Furosemide and Human Albumin for Treatment of Cirrhotic Ascites: Useful or Harmful?

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Abstract

Background: About half of cirrhotic patients develop ascites. Large volume paracentesis or trans internal jugular portosystemic shunt are alternatives in patients with refractory ascites. Intravenous (IV) loop diuretics are not routinely recommended for the treatment of cirrhotic ascites. We audited our experience with the use of IV furosemide and IV human albumin for the treatment of cirrhotic ascites that did not respond to oral diuretics and salt restriction. We also assessed the treatment side effects and patient's outcomes. **Patients and Methods:** Study subjects were selected from patients who were admitted for management of moderate or massive cirrhotic ascites refractory to oral diuretics and salt restriction. Patients' characteristics were documented. Renal function and electrolytes were measured on admission and daily thereafter. All patients were treated with IV furosemide at 40-60 mg TID, human albumin at 100ml of 20% (20gm) per day and spironolactone at 150-400 mg daily. We recorded complications and mortality during these ad-

missions. **Results:** Fifty admission episodes for 28 patients were evaluated. The mean age was 58 ± 5 years. In 32 admissions, the ascites responded to the treatment regimen and Large volume paracentesis (LVP) was not required. The mean serum creatinine was $132 \pm 17 \mu\text{mol/l}$. High urine sodium was an indicator of response, with a mean of $71 \pm 14 \text{ mmol/l}$. Mild renal impairment was the most common complication (53.3%). The mean duration of hospital stay was 9.2 ± 2.3 days. Seven patients died from sepsis and hepatorenal syndrome type 1. **Conclusions:** Closely monitored use of IV furosemide with human albumin for treatment of cirrhotic ascites is effective and superior to oral diuretics, and it may reduce the need for LVP.

Key Words: Hyponatremia, Renal impairment, Hypokalemia, Spironolactone, Hepatorenal syndrome.

Abbreviations: TIPS- trans internal jugular portosystemic shunt, LVP- large volume paracentesis, CHC- chronic

hepatitis C, HRS1- hepatorenal syndrome type I

Introduction

Liver cirrhosis is the most common cause of ascites, and 50% of cirrhotic patients will develop ascites within 10 years (1). The pathogenesis of ascites is complex. Development of ascites is the outcome of multiple factors, including arterial vasodilatation that impairs the renal blood flow (2,3), high sinusoidal capillary pressure secondary to portal hypertension (PHTN) (4) and splanchnic vasodilatation from neurohumoral activation via mainly nitric oxide (5,6). Hypoalbuminemia resulting from impaired hepatic synthetic function will lower the oncotic pressure and aggravate fluid leakage into the third space (7). Currently, arterial vasodilatation is accepted as the first triggering mechanism for salt and water retention in cirrhotic patients (2,3). These systemic changes make the management of the volume status in patients with cirrhotic ascites challenging and make the case for close monitoring. Salt restriction, bed rest, and potassium-sparing diuretic spironolactone are usually sufficient in patients with mild cirrhotic ascites (6,8), but in patients with moderate to massive ascites, a loop diuretic (furosemide) is often added orally. The maximum accepted diuretic doses are 400 mg for spironolactone and 160 mg for furosemide per day (9,10). The efficacy of oral diuretics in the treatment of massive cirrhotic ascites is reduced because of intestinal wall edema secondary to portal hypertension and hypoalbuminemia (11). Additionally, impaired albumin function can alter albumin drug binding and may result in the abnormal bioavailability of diuretics (12). Many patients will not respond to oral diuretics and will need therapeutic paracentesis (9,10). Currently, IV furosemide and other loop diuretics are not recommended in the treatment of cirrhotic ascites due to the risk of complications such as renal impairment, electrolyte imbalance and hepatic encephalopathy. Human albumin was found to enhance the response to diuretics and to reduce recurrence of ascites (13). Data on the use of IV furosemide in cirrhotic patients with ascites, with or without human albumin, is limited to testing the diuretic's response by measuring urine sodium after the administration of a single dose of intravenous furosemide (14-16). In this study, we evaluated the use of intravenous furosemide and human albumin in cirrhotic patients with ascites refractory to oral diuretic therapy and salt restriction.

Patients and Methods

Study design and aims

This is a prospective study aiming to firstly evaluate the ef-

fectiveness of intravenous furosemide and intravenous human albumin for the treatment of clinically and ultrasound-diagnosed moderate or massive cirrhotic ascites that were not responding to salt restriction measures and maximum tolerated oral diuretics and secondly assess the treatment complications and patient outcomes.

Study population

Patients with liver cirrhosis characterized by Child-Pugh scores B or C and with ascites that required admission to the hepatology unit (King Abdu Aziz University Hospital, Jeddah, Saudi Arabia, March 2008 to February 2009) were studied. Patients were included if they failed to respond to initial treatment with salt restriction, bed rest and maximum tolerated oral diuretics (all patients had daily doses of oral furosemide at 160mg and spironolactone at 150-400mg according to the serum potassium levels), as assessed by daily weight and 24-hour urine output measurements. The study was approved by the local ethics committee. All patients signed informed consent for the study. Patients were excluded if they had chronic renal failure defined as baseline serum creatinine higher than 140 $\mu\text{mol/L}$.

Assessments

Demographic data was obtained on all patients. Age, gender, cause of illness, and severity of disease (child-Pugh score) were recorded. Data on patients' presenting symptoms and their duration were recorded. We included abdominal distention, abdominal pain, fever, hematemesis, melena, and hepatic encephalopathy. We also obtained data on previous admissions for the treatment of ascites and the history of hepatocellular carcinoma (HCC) if previously diagnosed. On admission, vital signs were recorded as well as examination for severity of ascites, presence of spontaneous bacterial peritonitis (SBP), and/or presence of hepatic encephalopathy (HE). All patients were placed on a salt-restricted diet, together with protein restriction in patients with HE. All patients were monitored for daily weight and fluid intake and output.

Using the dimension clinical chemistry system Flex reagent cartridge, renal function was assessed. Diagnostic ascetic aspiration, ascetic fluid cultures and blood from patients with suspected SBP were also taken on admission. Urine samples for measuring urine sodium in mmol/L were obtained after at least 24 hours of IV furosemide and albumin administration. Abdominal ultrasound examinations were done if they had not been performed shortly prior to admission. We calculated the average serum sodium, creatinine

and potassium levels during each admission. Using the clinical and laboratory results, the Child-Pugh score was calculated for each patient at the time of admission.

Intervention

Patients who failed to respond to the maximum tolerated doses of oral furosemide and spironolactone, as assessed by failure to achieve negative fluid balance and weight reduction on daily weight monitoring, were shifted to IV furosemide at 40 mg twice daily and gradually increased to 60 mg three times per day. Spironolactone was continued at the maximum tolerated dose according to the serum potassium levels. (150-400 mg/day). Human albumin (20%) was given at a dose of 100 ml (20gm) daily during the treatment with IV furosemide. We defined the treatment response as a daily reduction of the patient's weight by 0.5-1 kilogram per day or a negative fluid balance of 500-1000 ml per day until the ascites clinically improved. For patients who failed to respond to the treatment or who did not tolerate the treatment because of renal impairment, LVP was done, and 50 ml (10gm) of human albumin was given for each liter of drained ascetic fluid. We reported the episodes and numbers of LVP.

Monitoring

Patients were monitored for treatment side effects, and withdrawal from the study. Medications that are known to impair renal function, like non-steroidal anti-inflammatory medication and aminoglycosides, were avoided during the admission. In patients who achieved a treatment response, the intravenous furosemide was gradually reduced and then shifted to oral administration at 40 mg two or three times per day. In patients who had normal baseline renal function and who had treatment-induced increased serum creatinine ≥ 140 $\mu\text{mol/L}$, the IV furosemide was discontinued. Similarly, in patients with mild baseline renal impairment, if the serum creatinine increased to ≥ 15 nmol/L , the IV furosemide was discontinued. All mortalities and their causes

during the admission episodes were recorded.

Statistical analysis

SPSS (version 115, Chicago, USA) was used for statistical analysis. Data were expressed in terms of the means \pm standard deviations or frequencies. Pearson's correlation analysis was used to explore relationships between the baseline, mean and discharge serum sodium levels, as well as the relationship between the baseline, mean and discharge serum creatinine levels. Kendall's and Spearman's correlation to define the relationships between baseline creatinine and renal impairment during the admissions. For testing the survival with respect to spontaneous bacterial peritonitis, Kaplan-Meier analysis was utilized.

Results

Frequency and severity of liver disease

Data is collected from 50 admission episodes for 28 individual patients. The mean age was 58 ± 5 years. Nineteen patients were male and nine were female. The most common diagnosis in our patients was chronic hepatitis C (CHC), followed by chronic hepatitis B (CHB), cirrhosis due to nonalcoholic fatty liver disease, hemochromatosis, and autoimmune hepatitis (AIH) (Table 1). Twenty-seven patients had a Child-Pugh score class C and only one patient had a Child-Pugh score class B. One patient had previous frequent admissions for LVP. Eight patients had a history of two or more previous admissions for medical treatment of ascites, five patients had one admission and fourteen patients had never before been admitted for the treatment of ascites. The mean duration of abdominal distension before admission was 25.1 ± 7.5 days. Ascites was massive clinically and by ultrasound examination in 42 admission (84%). In 23 patients (82%) serum albumin levels were lower than 25 g/L (normal 35-50 g/L).

Therapeutic strategy

LVP was done once during 7 admissions and 2-3 times

Table 1. Patients characteristics in total and by gender.

	Underlying pathology					Mean age in years	Total
	CHC	CHB	NAFLD	Hemochromatosis	AIH		
Male	12	5	1	1	0	55.9 ± 11.6	19
Females	7	0	1	0	1	61.7 ± 15.6	9
Total	19	5	2	1	1	-	28

CHC: Chronic hepatitis C; CHB : Chronic hepatitis B; NAFLD: Non alcoholic fatty liver disease, AIH: Autoimmune hepatitis

during 11 admissions. Nine were in patients with baseline serum creatinine levels greater than 130 $\mu\text{mol/L}$. In 32 admissions LVP was not required. The mean serum sodium level during the admission was 133 ± 2 mmol/L (Table 2). The mean serum sodium during admission and on discharge correlated significantly with the baseline serum sodium at admission ($rr = 0.34$, $P=0.049$, and $rr = 0.34$, $P=0.049$, respectively). The mean serum creatinine level during admission was 132 ± 17 $\mu\text{mol/L}$. Similar to the serum sodium, the mean serum creatinine during admission and on discharge had a direct correlation to the baseline creatinine ($rr 0.78$, $P<0.001$ and $rr 0.81$, $P>0.001$, respectively). The mean urine sodium after the exclusion of the four patients with HRS was 71 ± 14 mmol/L . Patients with refractory ascites who required LVP had a mean urinary sodium of 38.5 mmol/L . Six patients had nine episodes of sepsis and hypotension on admission; one of them had this during all three of his admissions, another patient had two attacks and four patients each had one episode of sepsis. We diagnosed SBP by positive ascetic fluid culture or high ascetic fluid cell count or both in 17 (34%) admissions. Patients with SBP were more likely to have hyponatremia compared to patients without SBP ($rr 0.74$ and 0.75 according to Kendall's and Spearman's correlations, respectively ($P = 0.05$ for both)).

Clinical outcomes

Seven episodes of variceal bleeding occurred during the study period. A single patient with massive ascites and HCC had four attacks during four out of five admissions. Three other patients had one attack of variceal bleeding each. Hepatic encephalopathy of variable severity from stages 1-4 as a presenting symptom was present in 22 admissions, and it was more likely to develop in patients with advanced disease, SBP and HCC. Three patients had HCC. Four patients had HRS type 1. Treatment was discontinued in four patients with SBP who developed HRS type 1 and in one patient with SBP and sepsis-induced acute tubular necrosis (ATN). In the remaining 45 admissions, mild reversible renal impairment was the most common complication, occurring in 24 admissions (53.3%). The baseline serum creatinine level correlated significantly with the development of renal impairment ($rr 0.58$ and 0.721 according to Kendall's and Spearman's correlations, respectively, and $P<0.001$ for both). Hypokalemia was the second most common complication, occurring in 9 of 45 admissions (20%); hypokalemia was correctable with oral potassium supplementation in all patients. Spironolactone was discontinued in 4 patients because of hyperkalemia.

Seven patients died during hospital admission from complications of SBP and sepsis, four from HRS type 1, one from ATN, and two patients from septic shock but without significant renal impairment. SBP significantly affected mortality ($rr -0.32$ according to Kendall's and Spearman's correlations, with $P < 0.03$ and < 0.02 , respectively). The estimated duration to mortality during admission for patients admitted with SBP according to the Kaplan-Meier analysis was 20.4 ± 7.2 days. The mean duration of the hospital stay was 9.1 ± 2.3 days.

Discussion

This study showed that intravenous furosemide with intravenous human albumin is effective for treatment of oral diuretic-refractory cirrhotic ascites and reduced the need for LVP in most patients. Previously published data showed variable results. Some reports suggested favorable outcomes even with the use of oral diuretics (13). Whereas others showed no additional benefit for this combination (17). In a meta-analysis of the studies published on the use of furosemide and human albumin in nephritic syndrome and cirrhotic ascites from 1966-2002, Elwell and colleagues proposed that such combination should be reserved for patients with refractory ascites to the maximum dose of diuretics and for patients with severe hypoalbuminemia (18). All of our patients showed no response to maximum oral diuretics and salt restriction and nearly a quarter of them had severe hypoalbuminemia. Human albumin was found to be superior to other volume expanders in reducing LVP-induced hypotension (19). This may explain why none of our patients had significant hypotension requiring dose adjustment or cessation of the IV furosemide. Our results also showed that treatment-responsive patients were more likely to have higher urine sodium compared to non-responders, which is similar to previous reports (14,15). We reported SBP in 34% of admissions, which is less than the previously reported figure of SBP in patients with cirrhotic ascites of 26% (6,9). As per the APASL consensus report for the primary prophylaxis of gastroesophageal variceal bleeding in 2008, high intra-abdominal pressure from massive ascites increases the risk of variceal bleeding (20). In this study, we observed 7 episodes of variceal bleeding in patients with massive ascites. Fernandez-Esparrach et al. suggested that the maximum tolerated oral diuretic dose should be maintained after LVP in patients with cirrhotic ascites to avoid rapid reaccumulation of ascites (21). In our cohort, post-LVP patients were maintained at the maximum tolerated dose of oral diuretics after discharge to reduce the need for frequent LVP. Side effects here are the

potential risks of the treatment of cirrhotic patients with IV furosemide or other loop diuretics; in our study, all of the recorded side effects were mild and reversible. Mortalities during admissions were related to sepsis, HRS1 and HCC. Patients with SBP were more likely to have hyponatremia due to serum sodium less than 135 mmol/L, which occurred in 14 out of 17 admissions with SBP (82.3%). Previous reports on hyponatremia in patients with cirrhosis showed that low serum sodium is associated with higher rates of SBP and mortality (22-24).

In conclusion, closely monitored use of intravenous furosemide and human albumin for treatment of massive cirrhotic ascites is effective and superior to oral diuretic therapy. It reduces the need for therapeutic paracentesis. The associated treatment side effects are usually mild and reversible.

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