Hyponatremia: Clinical Associations, Prognosis, and Treatment in Cirrhosis

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Abstract

Hyponatremia has long been associated with worsened clinical outcomes in patients with cirrhosis and those awaiting liver transplant. However, in the last several years, new modalities of therapy, particularly aquaretics known as "vaptans," and comprehensive prognostic models have been increasingly studied in the hopes of bolstering serum sodium levels and altering liver transplant candidate status. To examine the most recent, comprehensive, and pertinent data, a systematic review of both prospective and retrospective studies available on MEDLINE was completed, which provided information detailing clinical associations, treatment, and prognoses seen in those with hyponatremia in cirrhosis. Clinical associations with hyponatremia in cirrhosis including hepatorenal syndrome and hepatic encephalopathy were identified. For hyponatremia in those awaiting liver transplant, tolvaptan is an effective agent in temporarily normalizing serum sodium levels with minimal risk of osmotic demyelination. Prognostic models incorporating serum sodium levels were better able to predict urgency and need for transplant; yet the benefits and posttransplant effects of redefining a liver allocation score have yet to be established.

Key words: *Hyponatremia, Cirrhosis, Outcomes*

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Introduction

Hyponatremia is a common electrolyte disturbance in patients with advanced liver disease.[1-4] In the setting of cirrhosis, hyponatremia can be classified as either hypovolemic hyponatremia, which occurs in the setting of overtreatment with diuretics or excessive losses from the gastrointestinal tract, or hypervolemic hyponatremia, which results in decreased effective circulating volume from increased arterial from splanchnic vasodilatation leading to excessive secretion of arginine vasopressin.[1,5,6]

Hyponatremia can occur both before and after liver transplant. Pretransplant, it is associated with several clinical manifestations of decompensation,[4,7,8] and the degree of hyponatremia may increase the accuracy of the model for end-stage liver disease (MELD) score to predict survival.[8-11] Treatment of hyponatremia has not been demonstrated to improve survival in patients with advanced liver disease, and rapid correction can lead to life-threatening neurologic complications.[12,13]

This systematic review focuses on the prevalence, clinical associations, treatment, and prognosis of hypervolemic hyponatremia in patients with liver disease. An algorithm will be developed to guide management based on best available data.

Methods

Search strategy and identification of studies

We searched database MEDLINE for all studies on hyponatremia in the setting of cirrhosis as related to clinical implications, prognosis, and treatment. We used combinations of the key words: "hyponatremia," "sodium," "liver cirrhosis," "prevalence," "incidence," "intensive care units," "hepatorenal syndrome," "ascites," "central pontine myelinolysis," "therapeutics," "prognosis," and "liver

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transplant." We also searched the bibliographies of identified review articles for additional studies.

Inclusion and exclusion criteria

Of the 125 publications screened, we included 95 studies published in scientific journals that provided information about pathophysiologic mechanisms behind hyponatremia in cirrhosis, associated clinical implications, various therapeutic options, and competing prognostic models. We also searched all article bibliographies for relevant articles. We excluded data from other populations commonly presenting with hyponatremia including heart failure and syndrome of inappropriate antidiuretic hormone secretion. We omitted studies with sample sizes with patient populations of under 100 and those with insignificant data unless no other data were available from larger trials.

Prevalence

The prevalence of hyponatremia may vary according to several factors such as clinical setting, disease severity, and country of origin. Overall, approximately half of all patients with cirrhosis have serum sodium concentrations of ≤ 135 mmol/L, and about 21% to 28% have values < 130 mmol/L.[1,3,5] Angeli and associates describe the prevalence in the inpatient setting is as high as 57% as compared with 40% in the outpatient setting.[1] Most studies examining those admitted for complications of cirrhosis, found 21.6% to 35% of the patients with hyponatremia, whereas only 13.5% to 14% were seen in the outpatient setting.[14-18]

Regarding liver disease severity, most inpatients with hyponatremia were classified as Child-Pugh Class C cirrhosis.[1] This association between liver disease severity and hyponatremia has been confirmed by other studies (Table 1).[1,4,9-21] When assessing the region or country of origin, the frequency of hyponatremia was lower in patients from Asia and South America than it was in Western and Central Europe and North America.[1] This finding raises the question of the role of diet and lifestyle on outcomes in hyponatremia in cirrhosis. Interestingly, no association has been demonstrated between the prevalence of hyponatremia and patients' age, sex, and cause of cirrhosis.[1]

Clinical Associations

Pretransplant

Hyponatremia appears to be associated with manifestations of decompensated liver disease such as ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome.[1,14,21] Angeli and associates noted that the greatest frequency of these complications occurred at sodium levels < 130 mmol/L.[1] However, because hyponatremia occurs in the setting of end-stage liver disease, it is hard to delineate whether a variety of clinical manifestations are truly a result of reduced serum sodium levels or worsening liver disease. Hyponatremia's role as either a marker for severity

Table 1. Studies Assessing Prevalence of Hyponatremia in Patients with Cirrhosis

Study	Child-Pugh Score	Child-Pugh Class			MELD
		Class A	Class B	Class C	Score
Angeli[1] (2006)					
> 135 mmol/L (n=497)		53 (10.7%)	280 (56.3%)	155 (31.2%)	
131-135 mmol/L (n=275)			14 (5.1%)	120 (43.6%)	130 (47.3%)
≤ 130 mmol/L (n=211)		2 (0.9%)	75 (35.5%)	126 (59.7%)	
Londoño[4] (2006)					
≥ 130 mmol/L (n=222)	8 ± 2				17 ± 5
< 130 mmol/L (n=19)	10 ± 2			20 ± 7	
Kim[20] (2009)					
> 135 mmol/L (n=497)		10 (10.2%)	56 (57.1%)	32 (32.6%)	13.9 ± 4.6
131-135 mmol/L (n=275)		1 (2.6%)	16 (41.0%)	22 (56.4%)	16.3 ± 5.2
≤ 130 mmol/L (n=211)		1 (2.0%)	12 (23.5%)	38 (74.5%)	17.2 ± 5.1
Jenq[21] (2010)					
> 135 mmol/L (n=59)	11.1 ± 2.1			29.4 ± 13.6	
≤ 135 mmol/L (n=67)	12.4 ± 2.3			52.9 ± 13.9	

Abbreviations: MELD, model for end-stage liver disease
Data presented as mean standard deviation

of liver disease or an injurious clinical entity in itself, raises the question of whether treatment of hyponatremia would alter the complications of cirrhosis and the overall long-term survival.[20]

Hyponatremia has been associated with worsening ascites and the development of hepatorenal syndrome.[17,22] In both clinical entities, the effective circulating volume is significantly decreased, culminating in a severe circulatory dysfunction causing hypoperfusion, markedly reduced glomerular filtration rate, and intrinsic damage to the kidneys. The relation between hepatorenal syndrome and hyponatremia may best be explained by an individual association to defective loss of solute-free water.[23,24] Nonetheless, serum creatinine should be closely monitored in the setting of hyponatremia and cirrhosis as an objective marker for development of hepatorenal syndrome.

Few studies exist examining neurologic symptomatology in the setting of hyponatremia in cirrhosis; however, most prominently, serum sodium has been implicated as a risk factor for hepatic encephalopathy.[25,26] Guevara and associates, in a small prospective study, noted an 8-fold increased risk of hepatic encephalopathy (adjusted hazard ratio, HR=8.36) in patients with hyponatremia.[27] Mechanistically, a hypo-osmotic extracellular environment as seen in hyponatremia causes free water to shift intracellularly. To counterbalance this, intracellular solutes and electrolytes, most immediately potassium, transfer extracellularly to create a hypo-osmotic environment similar to that of plasma, as an effort to decrease fluid shift and effectively cerebral edema.[28,29] Some evidence exists that patients with hyponatremia in cirrhosis have decreased intracellular organic osmolytes and, as a result, a debilitated capacity to adapt to such electrolyte abnormalities.[30,31] Whether there is a true relation between hyponatremia as a cause of, or merely an association with, altered neurotransmitters and hepatic encephalopathy, is unclear. Other studies have suggested metabolism of excess ammonia in cirrhosis yielding elevated intracellular glutamine levels and a low-grade cerebral edema from astrocyte swelling as an alternative or even secondary pathophysiologic mechanism for hyponatremia and hepatic encephalopathy. The low-grade edema is insufficient to cause elevations in intracranial pressure, but the astrocyte swelling otherwise induces encephalopathy.[5,32-34]

There are data to suggest an association between low serum sodium concentrations and spontaneous bacterial peritonitis as well as sepsis unrelated to spontaneous bacterial peritonitis. One hypothesis is endotoxemia from bacterial translocation as a cause of increased TNF-α and splanchnic vasodilatation, subsequently inducing decreased cardiac output, increased arginine vasopressin secretion, and worsened fluid status.[35-38]

The allocation of donor organs is determined by medical urgency or a patient's risk of death as defined by a calculated score incorporating international normalized ratio, creatinine, and serum bilirubin.[39-42] This prognostic indicator, known as the MELD score, was implemented in 2002. Numerous studies have shown serum sodium as an pretransplant and posttransplant predictor of morbidity and short-term mortality, independent of the MELD score, where both the MELD and serum sodium concentration were predictive of death at 90 days among patients on the liver transplant waiting list.[1,9,11,43-52]

The MELD score has been criticized for its limited prognostic accuracy for certain subgroups including patients with cirrhosis, complicated by ascites and hyponatremia.[9,43,49,53] Invariably, the predictability of MELD score is enhanced with the incorporation of sodium (Table 2).[9,43,46,48,49,51,54-58] Hence, several studies have incorporated serum sodium levels into the calculated MELD score as different models.[56,57,59] The most acknowledged prognosticator, the MELD-Na, has been used to assess and compare any changes in the accuracy of portending short-term mortality. A varying degree of improvement was seen, but each of these studies was limited by sample size.[43,47,49] Most recently, Kim and associates developed a well-powered multivariate survival model incorporating 13 940 registrants from the Organ Procurement and Transplantation Network comparing the MELD versus the MELD-Na scores' abilities to predict short-term mortality at 90 days after registration for the liver transplant waiting list.[8] The authors state that the MELD-Na score's predictability improved particularly at the lower MELD scores values, where less discrepancy existed between actual and predicted probabilities of death. The authors predicted that about 7% of deaths (90/1291) could have been prevented had the MELD-Na score been used. Yet, an allocation system that incorporates a factor with such wide variability

Table 2. Incremental Improvement in Predicting Patient Survival When Incorporating Serum Sodium

Study	Time point					
	3 Months		6 Months		12 Months	
	AUC	*P* Value	AUC	*P* Value	AUC	*P* Value
Renfrew[54] (2011)						
MELD	0.887					
MELD-NA	0.848	.294				
Biselli[55] (2010)						
MELD	0.759		0.724			
MELD-NA	0.798	.03	0.765	.011		
iMELD	0.806	.097	0.792	.006		
UKMELD	0.781	.489	0.748	.388		
Lv[56] (2009)						
MELD	0.82					
MESO	0.875					
Huo[57] (2008)						
MELD	0.773		0.735			
MELD-NA	0.801	.126	0.778	.001		
iMELD	0.807	.102	0.797	< .001		
MESO	0.784	.013	0.747	< .001		
Huo[58] (2007)						
MELD	0.78					
MESO	0.795	.675				
Londoño[47] (2007)						
MELD	0.79				0.76	
MELD-NA	0.83	.4			0.78	.14
Luca[48] (2007)						
MELD					0.75	
iMELD					0.81	
Wong[51] (2007)						
MELD	0.75				0.72	
MELD-NA	0.79	.004			0.75	.004
Biggins[43] (2005)						
MELD	0.883		0.871			
MELD-NA	0.897	.465	0.905	.249		
Ruf[49] (2005)						
MELD	0.894					
MELD-NA	0.905	.026				
Heuman[9] (2004)						
MELD			0.809			
MELD-AS			0.863	< .05		

Abbreviations: AUC, area under the receiver operating characteristic curve; iMELD, integrated MELD with sodium and age; MELD, model for end-stage liver disease; MELD-NA, MELD incorporating serum sodium; MESO, MELD to serum sodium ratio; UKMELD, United Kingdom MELD score
P value presented compared to MELD score.

depending on the use of diuretics and fluid status may prevent pretransplant deaths, but also may increase posttransplant mortality, as patients with pretransplant hyponatremia have been shown to have more complications as previously noted.[60,61]

Posttransplant

Hyponatremia appears to have clinical implications after liver transplant. Patients with hyponatremia before transplant were more likely to develop delirium, renal failure, and infectious complications within the first months after transplant.[7] Londoño and associates noted a 3-month survival rate of 84% in those with hyponatremia as compared with 94% in those without hyponatremia ($P < .05$).[4] A larger study of 5152 patients by Dawwas and associates reproduced this finding, demonstrating a higher risk-adjusted mortality at 3 years ([HR] 1.28; CI 1.18-2.04; $P < .002$) for hyponatremic patients.[62] Interestingly, both of these latter studies found that the excess mortality was limited to the first 90 days postoperatively (≤ 90 days: HR 1.55; 95% CI, 1.42-3.70; $P < .001$ vs > 90 days: HR 1.12; 95% CI, 0.55-2.29; $P = .8$). In a study by Yun and associates, patients with hyponatremia had longer hospital and intensive care unit stays (median, 17 days vs 14 days and 4.5 days vs 3.0 days).[63] There are conflicting data to suggest no association between hyponatremia at the time of transplant and postoperative outcomes; however, these studies were limited by sample size and statistically insignificant data. While several studies examining varying degrees of pretransplant sodium levels as related to posttransplant outcomes (Table 3) have shown that a normonatremic state did not significantly reduce posttransplant mortality,[4,7,62] no study to date has attributed correction of hyponatremia to direct improvement in post-transplant outcome.

The most common complication in the immediate postoperative period seen in 1 study was altered mental status.[7] A widely studied explanation is the rapid correction of hyponatremia in the immediate postoperative period, leading to osmotic demyelination.[64-67] Hyponatremia also may affect neurotransmission, contributing to the development of hepatic encephalopathy.[1,31]

Treatment

Treatment of hyponatremia is defined by several variables including clinical presentation (symptomatic vs asymptomatic), chronicity (acute vs chronic), and cause of hyponatremia. Yet some therapies administered in patients with normal serum sodium levels differ in those with hyponatremia in cirrhosis. For instance, in a symptomatic patient presenting with seizures or an altered mental status, 3% normal saline solution is administered to rapidly correct their electrolyte deficiency. In contrast, hypertonic saline

Table 3. Study Demographics Assessing Association Between Hyponatremia and Liver Transplant

Study	Serum Sodium Pretransplant (mmol/L)	MELD Score Pretransplant	Acute Rejection	Renal Failure	Time point			
					/ Month		3 Months	
					Mortality	*P* Value	Mortality	*P* Value
Londoño[4] (2006)	138 ± 3	17 ± 5	2 (10%)	7 (37%)			5%	
No hyponatremia at time of transplant (n=222)								
Hyponatremic at time of transplant (n=19)	125 ± 4	20 ± 7	50 (23%)	32 (14%)			16%	< .05
Hackworth[7] (2009)								
Never hyponatremic before transplant (n=123)	138 ± 3	15 ± 6	3 (2%)	9 (7%)	4%			
Resolved hyponatremia before transplant (n=56)	135 ± 3	22 ± 8	7 (13%)	15 (27%)	5%	NS		
Hyponatremic at time of transplant (n=34)	127 ± 2	19 ± 5	2 (6%)	9 (27%)	3%	NS		
Dawwas[62] (2007)								
Hypernatremia at time of transplant (n=81)	>145	21.1 ± 10.5	22 (26.8%)	10 (12.5%)			26%	< .001
No hyponatremia at time of transplant (n=3066)	135-145	15.8 ± 7.1	1122 (36.6%)	233 (7.6%)			7.70%	
Mild hyponatremia at time of transplant (n=1127)	130-134	18.4 ± 7.4	364 (32.3%)	116 (10.3%)			9.30%	.09
Severe hyponatremia at time of transplant (n=541)	< 130	22.3 ± 9.3	159 (29.4%)	107 (19.7%)			15%	< .001

Abbreviations: MELD, model for end-stage liver disease; NS, not significant
Data presented as mean standard deviation; *P* value presented compared to normal serum sodium.
Note: hyponatremia defined as ≤ 130 mmol/L

Table 4. Studies Assessing Safety and Efficacy of Vaptan Treatment of Hyponatremia in Patients with Cirrhosis

Variable	Ginès[5] (2008)			Okita[76] (2010)		Wong[77] (2011)		Cárdenas[74] (2012)	
	Placebo (n=28)	Satavaptan 5 mg/day (n=28)	Satavaptan 12.5 mg/day (n=26)	Satavaptan 25 mg/day (n=28)	Tolvaptan (n=17)	Placebo (n=230)	Satavaptan (n=232)	Placebo (n=57)	Tolvaptan (n=63)
Age (y)	55 ± 10	57 ± 8	56 ± 9	59 ± 10	57.6 ± 7.1	56.4 ± 9.2	56.6 ± 10.2	55 ± 9	52 ± 8
Sex									
Male	22 (78.6%)	16 (57.1%)	19 (73.1%)	20 (71.4%)	14 (82.4%)	168 (73.0%)	158 (68.1%)	38 (66.7%)	50 (79.4%)
Female	6 (21.4%)	12 (42.9%)	7 (26.9%)	8 (28.6%)	3 (17.6%)	62 (27.0%)	74 (31.9%)	19 (33.3%)	13 (20.6%)
Cause of cirrhosis									
Alcohol	21 (75.0%)	21 (75.0%)	23 (88.5%)	20 (71.4%)	5 (29.4%)	151 (65.7%)	148 (63.8%)	30 (52.6%)	34 (54.0%)
Hepatitis B					4 (23.5%)	20 (8.7%)	18 (7.8%)	2 (3.5%)	2 (3.2%)
Hepatitis C					6 (35.3%)	49 (21.3%)	61 (26.3%)	15 (26.3%)	19 (30.2%)
Other					2 (11.8%)	39 (17.0%)	38 (16.4%)	6 (10.5%)	4 (10.5%)
Child-Pugh Score	10.1 ± 1.7	9.8 ± 1.4	9.8 ± 1.8	9.9 ± 1.6		8.0 ± 1.6	7.9 ± 1.5		
Child-Pugh Class									
Class A								6 (10.5%)	11 (17.5%)
Class B								28 (49.1%)	33 (52.4%)
Class C						45 (19.6%)	33 (14.2%)	19 (33.3%)	16 (25.4%)
Serum sodium /(mmol/L)	126 ± 4	127 ± 5	128 ± 4	126 ± 6		137 ± 4.5	137 ± 4.2	128.6 ± 4.4	128.8 ± 4.3
MELD Score	18.1 ± 4.9	17 ± 4.4	16.9 ± 5.4	17.1 ± 3.9		13.1 ± 3.8	12.8 ± 4.4	16.3 ± 6.4	15.8 ± 5.0

Abbreviations: MELD, model for end-stage liver disease
Data presented as mean standard deviation

increases the incidence of edema and ascites in those with cirrhosis.[5] In addition, to avoid complications of overcorrection, patients with chronic hyponatremia should never be corrected more than 12 mmol in 24 hours and 18 mmol in 48 hours because of the potential risk of neurologic complications including central pontine myelinolysis.[12,13,68,69]

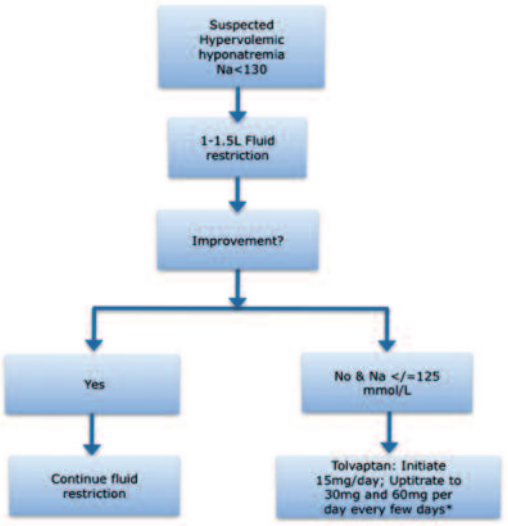
The goal in treating hypervolemic hyponatremia seen in cirrhosis is decreased solute-free water consumption or increased excretion. Hence, the total

volume of urine output and insensible losses must exceed free water intake, yielding a net negative balance. This objective is often achieved by fluid restriction of 1 to 1.5 L/d. However, studies have shown that effectiveness for this therapy is limited.[5,60,70] Another modality of therapy in patients with hypervolemic hyponatremia is to shift fluid back into intravascular space through the use of albumin. This method also has its limitations. While it has been shown to increase serum sodium,[71,72] its effects are transient. More recently, V2 receptor antagonists known as vaptans have become used increasingly in the therapy of hyponatremia in cirrhosis (Table 4).[73-77]

By selectively blocking V2 receptors in the principal cells of collecting duct, vaptans effectively increase the amount of solute-free water excreted from the body with a decrease in urine osmolality and subsequent improvement of hypervolemic hyponatremia.[5] Several agents exist in this class of medication; however, only 2, tolvaptan and conivaptan, have been approved by US Food and Drug Administration for treatment of hypervolemic hyponatremia, and only orally active tolvaptan has been approved for treating hyponatremia in cirrhosis (Figure 1).[74] The effect of vaptans is dose-dependent, starts 1 to 2 hours after administration, and lasts for 4 to 12 hours. Initiation of a vaptan requires strict monitoring of sodium levels in a hospital to prevent rapid correction or overcorrection.

Two multicenter, randomized, double-blind, placebo-controlled trials, the Study of Ascending Levels of Tolvaptan in Hyponatremia—SALT-1 and SALT-2—incorporating 448 primarily cardiac patients, have demonstrated tolvaptan's ability to significantly promote increases in serum sodium levels after 4 and 30 days.[78,79] A subgroup analysis of 63 cirrhotic patients, Cárdenas and associates, supported these findings, in which 41% vs 11% (P = .0002) reached normalization of serum sodium levels (> 135 mmol/L) at day 4 and 33% vs 19% (P = .0838) at day 30 in the tolvaptan-treated and placebo groups.[73] Currently, no data examining the long-term effects of tolvaptan on morbidity and mortality exist. Notably, about 7 days after withdrawal of tolvaptan, nearly 68% of patients had serum sodium levels that declined by at least 3 mmol/L, signifying a continued need for vaptan therapy.[73,74] In addition, other studies such as Okita and associates have suggested a dose-dependent improvement in

Figure 1. Proposed Algorithm for Treating Chronic Hyponatremia in Cirrhosis



*Note: There currently are no data regarding treatment with tolvaptan beyond 30 days.

ascites, lower extremity edema and tolerance to diuretics with tolvaptan, but further research is needed to confirm these findings.[60,61,76,79,80]

Conivaptan, approved for only 4 days of intravenous use in the hospital, for euvolemic and hypervolemic hyponatremia,[81] has limited data on its safety and efficacy.[82-84] In general, conivaptan was well tolerated with the most common adverse reaction being infusion-site reactions.[82,85] Conivaptan has been assessed in randomized double-blinded placebo-controlled clinical trials, only 1 of which used IV conivaptan.[83,86-88] Zeltser and associates used a small cohort of 84 patients with euvolemic or hypervolemic hyponatremia and randomly assigned them to 40 mg/d, 80 mg/d of IV conivaptan, or placebo, with outcomes measures including net increase in sodium levels and time from initial dose to ≥ 4 mEq/L increase. As compared with only 0.8 mEq/L with placebo, IV conivaptan significantly increased serum sodium levels during a 4-day treatment period, with 6.3 mEq/L and 9.4 mEq/L with 40 mg and 80 mg dosages. However, few patients had underling cirrhosis as the cause of hyponatremia (< 9 of 29 study population.[86] Interestingly, in an open-label multicenter trial involving 251 hospitalized patients, increases in serum sodium level from conivaptan use persisted through day 34, suggesting more long-term effects of IV conivaptan.[89] However, because conivaptan also has activity against V1R, causing vasodilatory effects in the portal and

splanchnic circulation, it theoretically has an increased risk of variceal bleeding.[90,91]

Another aquaretic, satavaptan, has been demonstrated as having a good effect on serum sodium levels.[75,92] In addition, several short-term studies show improved control of ascites with lower recurrence rates and decreased frequency of paracenteses.[75,93] However, most recently, Wong and associates reported 3 randomized double-blind studies incorporating 1200 patients, in which the first study compared satavaptan to placebo, and the following studies examined difficult-to-treat ascites, with and without concurrent diuretic therapy. Mortality was higher in patients treated with satavaptan than with placebo (HR 1.47; 95% CI 1.01-2.15). The authors concluded that satavaptan, alone or with diuretics, did not benefit the long-term management of ascites in cirrhosis.[77]

The most-frequent adverse effects of vaptans are thirst and dry mouth, seen in up to 29% of patients in published randomized controlled trials.[73] More detrimental adverse effects included dehydration, acute renal failure, orthostatic hypotension, encephalopathy, and hyperkalemia.[79,93,94] To effectively use this class of agents, more adequately powered studies to compare agents, to examine combinations, and to assess improvements in morbidity, mortality, and measures of cost/benefit, are required.

Conclusions

Presence of hypervolemic hyponatremia in the setting of end-stage liver disease forecasts worsened outcomes in both before liver and after liver transplant settings with increased associations with hepatic encephalopathy, hepatorenal syndrome, mortality, and longer hospital stays. Various prognostic models incorporating serum sodium levels are currently being trialed; yet, there is no clear evidence to suggest that incorporation and even correction of serum sodium affects overall mortality, but instead shifts the number of deaths from pretransplant to posttransplant. More research is required in this area. Despite this, traditional treatment modalities are slowly being replaced by vaptans. A growing body of evidence supports the efficacy and safety of tolvaptan, the only FDA-approved agent specifically for hyponatremia in cirrhosis. Current evidence shows that a statistically significant achievement of a normonatremic state is possible with tolvaptans compared to placebo and that maintenance requires continued use of tolvaptan. However, longer-term studies are lacking and more data examining tolvaptan's effects on other hyponatremia-related clinical implications are needed.

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