Serum sodium as a predictor to the outcome of critically ill cirrhotic patients

Thesis

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List Of Abbreviations

Abbr.	Full term
ADH	Antidiuretic hormone
AMP	Adenosinemonophosphate
AVP	Arginine vasopressin
CD	Collecting duct
CHF	Congestive heart failure
CL	Confidence interval
CL-	Chloride
CNT	Connecting tubule
CPM	Central pontine myelinosis
CPS	Child —Pugh score
DCT	Distal collecting tubule
DH	Dilutional hyponatremia
DS	Standard deviation
ECF	Extracellular fluid
ECFV	Extracellular fluid volume
GFR	Glomerular filtration rate
HBV	Hepatitis B
HCV	Hepatitis V
HE	Hepatic encephalopathy
HRS	Hepatorenal syndrome
HVPG	Hepatic venous pressure gradient
ICF	Intracellular fluid
INR	International normalized ratio

K+	Potassium
LFT	Liver function test
Na+	Sodium
NO	Nitrous oxide
ODS	Osmotic demyelinating syndrome
PH	Portal hypertension
PKA	Protein Kinase A
RFT	Renal function test
SIADH	Syndrome of inappropriate ADH secretion
TALH	Thick ascending loop ofHenle
TIPS	Transjugularintrahepatic portosystemic shunting
V2R	Type 2V2 receptor

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Introduction

Cirrhosis is characterized by a progressive circulatory dysfunction, including systemic arterial vasodilatation and reduced peripheral resistance, which induces renal hypo-perfusion. Renal hypo-perfusion represents the stimulus that activates the renin-angiotensin-aldosterone system having sodium and water retention consequence (**Gines and Guevara, 2008)**.

Hyponatremia in cirrhosis is defined as serum sodium level below 130 mmol/l. According to this definition, the prevalence of hyponatremia in cirrhotic patients is about 21.6%. If the cut-off limit for serum sodium is considered to be of 135 mmol/l (that represents the lower limit of serum sodium in healthy subjects), the prevalence will reach about 49.4%(**Angeli et al,2006).**

Cirrhotic hyponatremia is associated with hepatorenal syndrome, jaundice, hepatic encephalopathy and refractory ascites. Serum sodium in cirrhosis that is below 130 mmol/l is associated with a median transplant-free survival of less than 6 months (**Heuman et al,2004).**

Hepatorenal syndrome in cirrhotic patients is characterized by intense stimulation of the renin angiotensin aldosterone system due to an extreme systemic vasodilatation. In this situation, probably, hyponatremia is due to increased levels of arginine vasopressin and to reduced glomerular filtration rate and increased proximal tubular sodium reabsorption (**Gines et al, 2006).**

Several lines of evidence support the existence of a correlation between hyponatremia and hepatic encephalopathy. Levels of serum sodium and ammonia may determine the major electroencephalographic changes in cirrhosis (**Amodio et al, 2001).**

The novel theories suggest that low-grade cerebral oedema which can be induced by hyponatremia may play a part in the pathogenesis of hepatic encephalopathy,This low-grade cerebral oedema resulting from the swelling of astrocytes [maybe by increased intracellular content of glutamine, resulted from ammonia metabolism] is responsible for a number of alterations of the neurological functions, which can lead to hepatic encephalopathy. In this context of the existence of low-grade cerebral oedema, hyponatremia plays an important role in increasing the osmotic pressure on the astrocytes. In this situation, only small increases in ammonia levels can induce clinically manifested hepatic encephalopathy(**Haussinger,2006).**

Cirrhotic hyponatremia affects the quality of life of the patients because they require a fluid intake restriction in order to prevent further dilution, and is usually not very well tolerated. In a recent study, hyponatremia was an independent predictive factor of the altered quality of life in a patient with cirrhosis (**Konstam et al, 2007).**

In view of the above low serum sodium level in critically ill cirrhotic patients are associated with high complications of liver cirrhosis and in-hospital mortality. So we hypothesized that sodium level could be used as a predictor to the outcome of cirrhotic patients who admitted to ICU.

Aim Of Work

The aim of this study is to evaluate the serum sodium levels as a predictor to the outcome of critically ill cirrhotic patients.

SODIUM DISORDERS

Disorders of serum Na^+ concentration are caused by abnormalities in water homeostasis that lead to changes in the relative ratio of Na^+ to body water. Water intake and circulating Arginine vasopressin [AVP] constitute the two key effectors in the defense of serum osmolality; defects in one or both of these defense mechanisms cause most cases of hyponatremia and hypernatremia.

Notably, volume status also modulates the release of AVP by the posterior pituitary so that hypovolemia is associated with higher circulating levels of the hormone at each level of serum osmolality. Similarly, in hypervolemia causes of arterial underfilling, e.g., heart failure and cirrhosis, the associated neurohumoral activation is associated with an increase in circulating AVP, leading to water retention and hyponatremia. Therefore, a key concept in sodium disorders is that the absolute plasma Na^+ concentration tells one nothing about the volume status of a specific patient; this must be taken into account in the diagnostic and therapeutic approach (**Verbalis, 2011)**.

HYPONATREMIA: AN OVERVIEW

Hyponatremia is an electrolyte disturbance in which the sodium concentration in the serum is lower than normal. Hyponatremia is defined as aplasma Na^+ concentration <135mEq/L (**Adrogué and Madias, 2005; David et al, 2012)**.

Hyponatremia is a very common disorder, occurring in hospitalized patients. This disorder is almost always the result of an increase in circulating AVP and/or increased renal sensitivity to AVP, combined with any intake of free water. Hyponatremia can therefore occur by an

increase in Total Body Water [TBW], a decrease in body solutes (either Na^+ or K^+), or any combination of these. In most cases, more than one of these mechanisms is operant **(Schrier et al, 2013)**

CLASSIFICATION OF HYPONATREMIA

An assessment of Extracellular Fluid [ECF] volume provides a useful working classification of Hyponatremia as it can be associated with decreased, normal, or high total body sodium **(Parikh et al,2007)**. So it can be classified into:

(1) Hyponatremia with ECF volume depletion.

(2) Hyponatremia with excess ECF volume.

(3) Hyponatremia with normal ECF volume.

HYPOVOLEMIC HYPONATREMIA

Hypovolemia causes marked neurohumoral activation, increasing circulating levels of AVP. The increase in circulating AVP helps preserve blood pressure via vascular and baroreceptor VIA receptors and increases water reabsorption via renal V2 receptors; activation of V2 receptors can lead to hyponatremia in the setting of increased free-water intake (**Adrogué and Madias, 2000**).

Non-renal causes of hypovolemic hyponatremia include gastrointestinal (GI) loss (vomiting, diarrhea, tube drainage and insensible loss (sweating, burns) of Na^+-CI^- and water in the absence of adequate oral replacement; urine Na^+ concentration is typically <20 mEq/L. Notably, these patients may be clinically classified as euvolemic, with only the reduced urinary Na^+ concentration to indicate the cause of their hyponatremia (**Verbalis and Berl, 2008).**

The renal causes of hypovolemic hyponatremia share an inappropriate loss of Na^+-Cl^- in the urine, leading to volume depletion and an increase in circulating AVP; urine Na^+ concentration is typically >20 mEq/L. A deficiency in the circulating aldosterone and/or its renal effects can lead to hyponatremia in primary adrenal insufficiency and other causes of hypoaldosteronism; hyperkalemia and hyponatremia in a hypotensive and/or hypovolemic patient with high urine Na^+ concentration (>20 mEq/L) should strongly suggest this diagnosis. **(Milionis et al, 2002)**

Salt-losing nephropathies may lead to hyponatremia when sodium intake is reduced due to impaired renal tubular function. Typical causes include reflux nephropathy, interstitial nephropathies, post-obstructive uropathy, medullary cystic disease, and the recovery phase of acute tubular necrosis **.(Milionis et al, 2002).**

HYPERVOLEMIC HYPONATREMIA (Dilutional hyponatremia)

Patients with hypervolemic hyponatremia develop an increase in total body Na^+-Cl^- that is accompanied by a proportionately greater increase in total body water exceeds that of Na^+, leading to a reduced plasma Na^+ concentration.

As in hypovolemic hyponatremia, the causative disorders can be separated by the effect on urine Na^+ concentration, with acute or chronic renal failure uniquely associated with an increase in urine Na^+ concentration. With exception to renal failure, these states are characterized by sodium retention(urinary Na^+ concentration<10 mEq/L) (**Verbalis, 2011).**

EUVOLEMIC HYPONATREMIA

Patients and experimental animals with hypothyroidism often have impaired water excretion and sometimes develop hyponatremia. The dilution defect is reversed by treatment with thyroid hormones. Both decreased delivery of filtrate to the diluting segment and persistent secretion of AVP, alone or combination, have been proposed as mechanisms responsible for the defect **(Sterns et al, 2009).**

Severe hyponatremia also can be a consequence of secondary due to pituitary disease; **(Schrier, 2006**; **Schrier et al,2006)** whereas the deficit in circulating aldosterone in primary adrenal insufficiency causes hypovolemic hyponatremia, the predominant glucocorticoid deficiency in secondary adrenal failure is associated with euvolemic hyponatremia (**Diederich et al,2003**; **Olchovsky et al, 2005)**.

Glucocorticoids exert a negative feedback on AVP release by the posterior pituitary so that hydrocortisone replacement in the patients will rapidly normalize the AVP response to osmolality, reducing circulating AVP.

The syndrome of inappropriate antidiuresis is the most common cause of euvolemic hyponatremia**(Palmer et al 2003).**

DIAGNOSIS OF HYPONATREMIA

Figure 1 illustrates the outline of diagnostic approach of hyponatremia

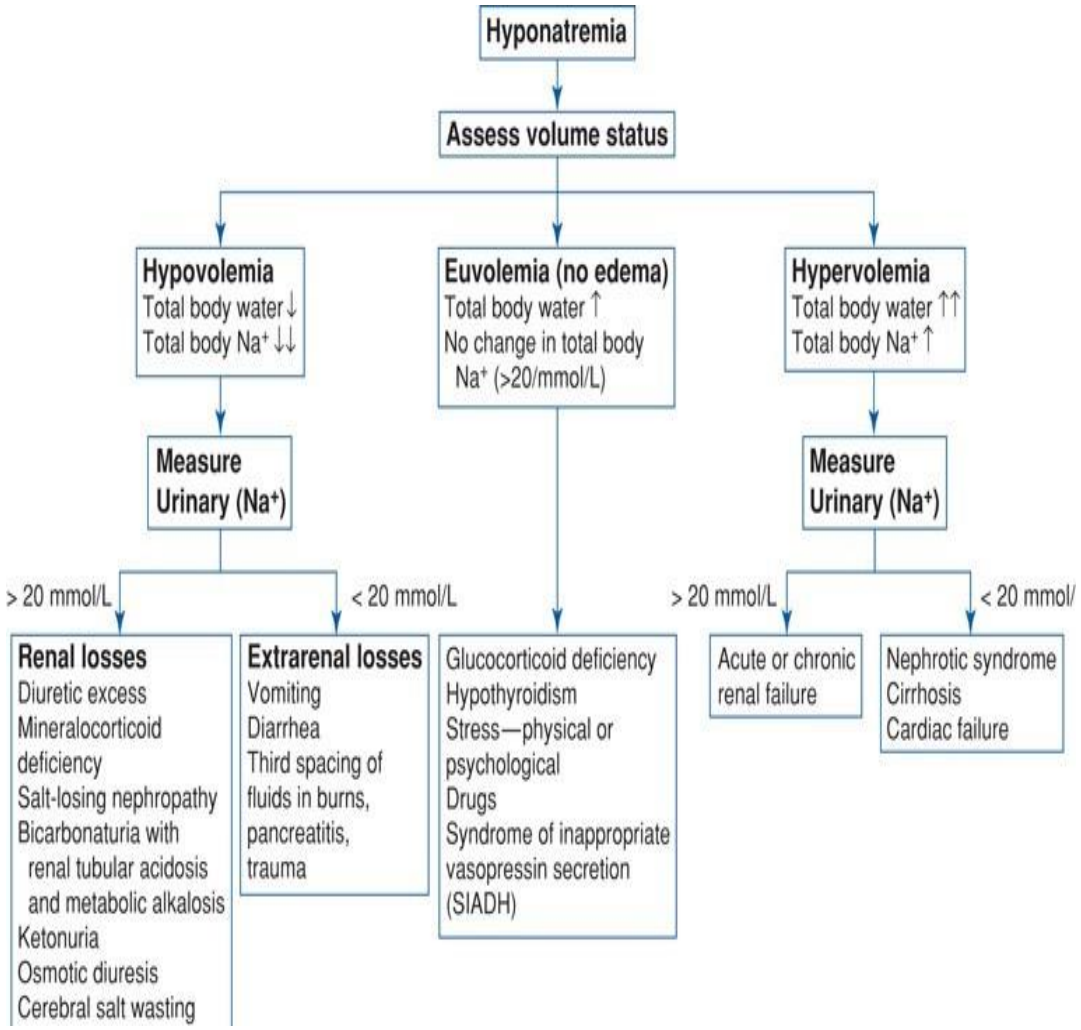

Figure 1: Diagnostic approach of hyponatremia **(Verbalis, 2011).**

HYPONATREMIA IN CIRRHOSIS

Hyponatremia is a frequent complication of advanced cirrhosis related to an impairment in the renal capacity to eliminate solute-free water that causes a retention of water that is disproportionate to the retention of sodium ,thus causing a reduction in serum sodium concentration and hypo-osmolality (**Angeli et al, 2006).**