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Efficacy of Combination Therapy with Natriuretic and Aquaretic Drugs Compared to A Conventional Diuretic Therapy as Treatment of Cirrhotic Patients with Ascites and Hyponatremia: An Evidence based Case Report

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Abstract: ***Introduction****: Cirrhotic patients with ascites and hyponatremia have a poor quality of life and high mortality. Classic diuretics such as furosemide and aldosterone antagonists spironolactone improve water retention and edema, but exacerbate hyponatremia in cirrhotic patients.* ***Case illustration****: 62 years old male presented to our hospital with severe abdominal pain and severe hyponatremia caused by cirrhosis hepatic. The patient already treated with a conventional diuretic therapy. We would like to investigate the efficacy between conventional diuretic therapy with natriuretic only and combination therapy with natriuretic and aquaretic drugs in treatment of our patient.* ***Method****: We search article in PubMed and Proquest, we found 3 eligible Randomized-Controlled Trial (RCT). We do critical appraisal using Center of Evidence-Based Medicine (CEBM) tool from Oxford University.* ***Result****: In three trial study, compared to a conventional therapy with only natriuretic drugs, a combination therapy with natriuretic and aquaretic drugs is more effective for patients with cirrhotic ascites. The six-month survival may be improved in cirrhotic patients with hyponatremia after tolvaptan short administration,* ***Conclusion****: combination therapy with natriuretic and aquaretic drugs is more effective compered to conventional therapy with only natriuretic drugs for patients with cirrhotic ascites*

Keywords: Diuretic, tolvaptan, ascites, cirrhosis

1. Introduction

Cirrhotic patients with ascites and hyponatremia have a poor quality of life and high mortality [1]. One year survival rate in these patients is less than 60% [2]. Development of ascites with or without hyponatremia is associated with multiple pathophysiological alteration, i.e. renal water and sodium retention, hyperdynamic cardiovascular dysfunction secondary to arterial splanchnic vasodilation, activation of the renin-aldosterone system, and increased aldosterone and vasopressin levels in the peripheral circulation [3, 4].

Classic diuretics such as furosemide and aldosterone antagonists spironolactone improve water retention and edema, but exacerbate hyponatremia in cirrhotic patients [5]. Distinct from the classic diuretics, tolvaptan, a highly selective vasopressin V2 antagonist, effectively improves levels of serum sodium by increasing the excretion of electrolyte free water without altering total level of electrolyte excretion [6].

Tolvaptan (TLV) is a new oral, selective vasopressin V2 receptor antagonist originally developed for the treatment of hypervolemic or euvolemic hyponatremia in patients with heart failure, cirrhosis or syndrome of inappropriate antidiuretic hormone[7,8]. Inhibition of the vasopressin V2 receptor by TLV prevents the insertion of aquaporin 2 water channels into the apical cell membrane of the collecting duct, which increases free water excretion without significantly affecting urinary sodium or potassium secretion[9]. This allows for reduced water retention with elevated serum sodium levels, which is an ideal outcome in decompensated liver cirrhosis patients with refractory ascites.

2. Case Illustration

62 years old male presented to our hospital with severe abdominal pain. He had no history of alcohol consumption or cigarette smoking, and his family history was not significant. From the physical examination, his lung was in normal limit, abdominal examination obtained a moderate-severe ascites. From laboratory finding, his protein total was 6,1 g/dL, albumin level 1,3 g/dL, globulin level 4,1 g/dL, renal function was in normal limit, electrolyte serum showed decreased of natrium level 123 mmol/L. He continued to receive oral furosemide (40 mg) and spironolactone (100 mg) daily for ascites retention. We try to think about the best treatment for him, since there was a severe hyponatremia is diuretic only still safe for him? Or whether we need to modify his therapy.

3. Method

The article searching was conducted in PubMed and Proquest as search engines on 10th July 2019. We are using advanced search with keywords “tolvaptan” AND “diuretic” AND “ascites” AND “cirrhosis”. Inclusion criteria were: [1] Clinical trial that comparing the combination therapy with natriuretic and aquaretic drugs with a conventional diuretic therapy as treatment of cirrhotic patients with ascites and hyponatremia [2] Article is written in english or Indonesian; [3] Available in free full text; [4] Article is not published more than 10 years before searching time. The eligible

articles then being critical appraised by CEBM (Center of Evidence-Based Medicine) tool by Oxford University.

4. Selection

After doing the searching, based on title and abstract using inclusion criteria and exclusion criteria, three articles were obtained.

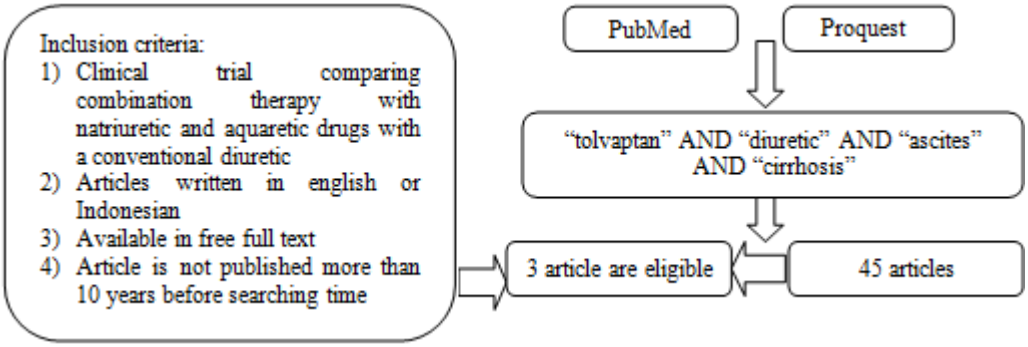

Figure 1: Our method to find articles

Critical Appraisal

After the selection, critical appraisal was done using several aspects based on Center of Evidence based Medicine, University of Oxford for therapy study (Table 1).

Table 1: Critical Appraisal of the usefull articles based on criterias by Centre of Evidence Medicine University of Oxford

			Validity				Relevance				
Articles (years)	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding	Comparable treatment	Intention to treat	Domain	Determinant	Measurement of outcome	Levels of evidence *
Uojima H et al. (2017)	RCT	56	+	+	-	+	+	+	+	+	2b
Ohki T et al. (2015)	RCT	120	+	+	-	+	+	+	+	+	2b
Wang et al. (2018)	RCT	230	+	+	+	+	+	+	+	+	1a

5. Result

Uojima H et al did a prospective study , randomized control trial to assess the effects of a combination therapy with natriuretic and aquaretic drugs in cirrhotic ascites patients. The primary endpoint of this study was the change in body weight from the baseline. A total of 56 patients were randomized to receive either tolvaptan (n = 28) or furosemide (n = 28). In the combination and conventional diuretic groups, the average decrease in body weight from the baseline was 3.21 ± 3.17 kg (P < 0.0001) and 1.75 ± 2.36 kg (P = 0.0006), respectively, when measured on the final dosing day. Following 1 week of treatment, a significantly greater reduction in body weight was observed in the combination diuretic group compared to that in the conventional diuretic group (P = 0.0412). In this study, hyponatremia and hypokalemia were not seen in the combination diuretic group. To avoid an electrolyte disturbance, combination diuretic therapy should be evaluated and may resolve hyponatremia with long-term treatment [10].

Ohki T et al also did a randomized control trial were performed in 120 refractory ascites patients. Sixty patients were treated with oral TLV at a starting dose of 3.75 mg/d in addition to sodium restriction (> 7 g/d), albumin infusion (10-20 g/wk), and standard diuretic therapy (20-60 mg/d furosemide and 25-50 mg/d spironolactone) and 60 patients with large volume paracentesis in addition to sodium restriction (less than 7 g/d), albumin infusion (10-20 g/wk), and standard diuretic therapy (20-120 mg/d furosemide and 25-150 mg/d spironolactone). Tolvaptan (TLV) was effective in 38 (63.3%) refractory ascites patients. The best cut-off values for urine output and reduced urine osmolality as measures of refractory ascites improvement were > 1800 mL within the first 24 h and > 30%, respectively. The serum sodium concentration increased, peaking 3 days after administration of TLV. The median elevated serum sodium concentration was 4.5 mEq/L. The cumulative incidence rate was significantly higher in the control group with a median incidence time of 30 d in the TLV group and 20 d in the control group. Administration of TLV results in better control of refractory ascites and reduced the incidence of additional invasive procedures or hospitalization compared with conventional ascites treatments [11].

Another randomized controlled trial were done by Wang et al. On their study they observed Two hundred forty-nine decompensated cirrhotic patients with or without hyponatremia. Patients were divided into two groups according to receiving either tolvaptan or placebo treatment for 7-day. Subsequently, the patients were followed up for 6 months. Two hundred thirty patients, including 98 with hyponatremia (tolvaptan vs. placebo: 69 vs. 29) finished the

study. Tolvaptan did not alter serum sodium levels and survival outcome of decompensated cirrhotic patients without hyponatremia. However, tolvaptan treatment remarkably improved serum sodium levels and six-month survival in patients with hyponatremia. Following tolvaptan treatment, serum sodium levels were restored to normal in 63.8% of patients, whereas in patients receiving placebo, only 36.2% showed the same effect (P< 0.05). Compared to a six-month survival rate of 68.97% in patients receiving placebo, the survival rate in tolvapatan-treated patients was 89.94% (P< 0.05). Furthermore, six-month survival rate in the tolvaptan-treated hyponatremia patients with resolved serum sodium was 81.32%, whereas the survival in those with unresolved serum sodium was only 24% (P< 0.05) [12]

6. Discussion

Hyponatremia is tightly associated with cirrhotic complications, including hepatic encephalopathy, refractory ascites, renal failure, spontaneous bacterial peritonitis, and hepatic hydrothorax, and concomitant high mortality [13]. Tolvaptan is a recently FDA approved drug used to treat hyponatremia in cirrhotic patients. The safety and effiacy of this drug in cirrhotic patients are not clarified yet. It is unknown to date whether tolvaptan treatment improves the survival of cirrhotic patients. It is also not clear whether tolvaptan has similar or different efficacy in cirrhotic patients with different degree of hyponatremia. A single-center retrospective study in Japan included 95 cirrhotic patients who received tolvaptan for ascites treatment [14]. Among patients with hyponatremia (serum sodium level < 135 mEq/L), 60.0% achieved a normal level after 1 week treatment, and the survival rate was significantly higher in patients with a normalized serum sodium level.

A several studies have evaluated the efficacy of tolvaptan for treating refractory ascites on cirrhosis patient with hyponatremia. Uojima H et al. on their study found that addition of tolvaptan had only a slight influence on ammonia levels, and that the incidence of hepatic encephalopathy was reduced in the tolvaptan group, compared to furosemide. Hepatic encephalopathy is related to impaired blood circulation, which decreases renal clearance of ammonia. In contrast to furosemide, tolvaptan increases urine output without decreasing renal blood flow, leading to indistinguishable ammonia levels in the tolvaptan group between the baseline and the final dosing day. On Their study has shown that addition of furosemide influenced 24-h CCr and plasma renin activity, with renal dysfunction more frequent in the furosemide group than that in the tolvaptan group.

However, Ohki Tet al. on their study stated that TLV administration deteriorated renal function. Although there is a possibility that TLV could lead to dehydration and decrease eGFR, progressive liver disease induces renal impairment, a phenomenon known as hepatorenal syndrome[16]. The control patients also had a significant decrease in eGFR during the follow-up period. These patients were treated with large-volume paracentesis under infusion of albumin, which was also reported to have less impact on renal function[17]. In a comprehensive manner, the decrease in eGFR did not depend on TLV but on progressive liver disease itself. Thus, we concluded that TLV could be used safely in patients with refractory ascites. A diuretic agent preferably should not activate the sympathetic nervous system or the RAAS, because the pathophysiology of ascites formation in liver cirrhosis is associated with the activation of the RAAS, and occurs to help restore blood homeostasis. Although concomitant medications such as branched-chain amino acids, nonabsorbable disaccharides, angiotensin II receptor blockers, or angiotensin converting enzyme inhibitors affect RAAS activation and ammonia levels, combination therapy including aquaretic and natriuretic drugs reduces the incidence of diuretic-related severe side effects. In contrast, increasing the dosage of furosemide above the ceiling dose increases the frequency of severe side effects. A combination therapy, including a vasopressin V2-receptor antagonist, which increases the serum sodium concentration, has the potential to improve outcomes in liver cirrhosis patients with ascites

Wang et al found that low dosage of tolvaptan (7.5 mg/day or 15 mg/day) treatment for 7 days significantly improved six-month survival of decompensated cirrhotic patient with hyponatremia. Compared to placebo-treated patients whose six-month survival rate was 68.97%, 89.94% of decompensated cir-rhotic patients with hyponatremia survived after tolvaptan treatment. Hyponatremic patients who restored normal levels ofserum sodium after tolvaptan treatment (tolvaptan re-sponders) demonstrated a six-month survival rate of 89.31%, whereas those with refractory hyponatremia (non-responders) only had a 24% survival rate. The base-line serum sodium levels were closely associated with the efficacy of tolvaptan. Compared to the impressive benefit of tolvaptan on cirrhotic patients with mild and moderate hyponatremia whose six-month survival rate was more than 50%, the drug seems to have limited effects on cirrhotic patients with severe hyponatremia. Among 6 patients with severe hyponatremia, only 2 patients survived and maintained normal serum sodium levels 6 months after tolvaptan treatment. It is unknown why severe hyponatremia in cirrhotic patients is difficult to treat with tolvaptan. The existence of an adaptive renal response to chronic hyponatremia, which results in a diminished response to a selective antagonist such as tolvaptan, might be an explanation [15].

7. Conclusion

It is recommended to use tolvaptan with dose 7.5 mg/day in addition to the natriuretic drug which was used prior. Based on current knowledge, hyponatremia is the most important factors affecting the prognosis of patients with cirrhosis and ascites. Resolved hyponatremia may directly reduce the risk of hepatic encephalopathy, hepatorenal syndrome and spontaneous peritonitis in decompensated cirrhotic patients, which may directly improve survival in patients who respond to tolvaptan treatment. This might partially explain why the survival is significantly improved in resolved hyponatremia patients following tolvaptan treatment.

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