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The effect of midodrine, octreotide and albumin in patients with refractory ascites

by

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Abstract

Refractory ascites and hepatorenal syndrome (HRS) are complications associated with cirrhosis. Management options for the two disorders include symptomatic therapy or management of portal hypertension by invasive or pharmacologic therapies. A systematic review of outcomes in HRS trials was prompted by the need to determine which endpoints to use in a prospective study of pharmacologic therapy for refractory ascites with or without HRS. From this review, it was determined that the existing literature is limited by poor study design, including non-randomization, heterogeneous study populations, lack of power, and limited use of clinically relevant outcomes. We went on to evaluate the role of midodrine, octreotide and albumin in 8 patients with refractory ascites. There was a beneficial effect on weight and naturesis but no change in renal function. Further studies are needed to clarify this potential benefit and the possibility of hepatic dysfunction on therapy, a novel observation of the study.

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List of Abbreviations

Blood pressure (BP)

Glomerular filtration rate (GFR)

Hepatorenal syndrome (HRS)

Interquartile range (IQR)

Kolmogorov-Smirnov (K-S)

Mean arterial pressure (MAP)

Model for End stage Liver Disease (MELD)

Modification of Diet in Renal Disease (MDRD)

Octreotide long acting release (octreotide-LAR)

Standard deviation (SD)

Tc-99m- diethylenetriaminepentaacetic acid (DTPA) renography

Transjugular intrahepatic portosystemic shunt (TIPS)

Vascular endothelial growth factor (VEG-F)

Chapter 1 - *Introduction*

1.1 The definition, stages and clinical impact of cirrhosis.

Cirrhosis, or end-stage scarring of the liver is the final common pathway of multiple hepatic insults. Cirrhosis can be divided into compensated or decompensated disease based upon the presence of ascites, variceal bleeding, jaundice or encephalopathy. Defined by the absence of these portal hypertensive complications, patients with compensated cirrhosis have a median survival of >12 years. Those with decompensated cirrhosis have a median survival of 1.5 years (1). Ascites, the development of free fluid in the peritoneum, is the most common complication announcing the decompensated state.

1.2 The clinical spectrum of ascites, refractory ascites and hepatorenal syndrome (HRS) and the clinical significance of renal dysfunction.

Ascites occurs in 50% of compensated cirrhotics 10 years after the diagnosis is made. (2) It is associated with a reduction in survival to 50% at 2 years and 20% at 5 years. (3-5) Ascites can range from uncomplicated diuretic-responsive disease to diuretic intractable/resistant ascites (refractory ascites) (6).

The initial management of all cirrhotic patients consists of a low sodium diet. This is sufficient to control ascites in only 10-20% of patients. The remaining patients are initiated on diuretics to promote naturesis and create a negative

sodium and water balance. These agents are titrated to a maximum dose of 160 mg/day of furosemide and 400 mg/day of spironolactone with a goal weight loss of 0.5 -1 kg per day (7). As cirrhosis becomes more advanced there is a progressive reduction in renal perfusion and an impaired efficacy of diuretics. This results in refractory ascites in 5-10% of patients. As initially defined in 1996 and subsequently revised in 2003, refractory ascites is resistant or intractable to maximal diuretic therapy (7,8). The majority (>90%) of refractory ascites cases are diuretic intractable (9).

- Diuretic resistance is defined as a lack of response to dietary sodium restriction (90 mmol/day sodium diet) and intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week.
- Diuretic intractable ascites is defined as that which cannot be mobilized or prevented because of diuretic-induced complications (renal insufficiency, electrolyte abnormalities, hepatic encephalopathy).
    - Diuretic induced hepatic encephalopathy is the development of encephalopathy in the absence of other precipitating factors.
    - Diuretic induced renal failure is defined as a doubling in serum creatinine and/or increase to > 177 μmoL/L.
    - Diuretic induced hyponatremia is a decrease in serum sodium concentration by greater than 10 mEq/L to <125 mEq/L.
    - Diuretic induced hypo or hyperkalemia is a potassium of <3.5 mmol/L or >5.5 mmol/L respectively (7,8).

Many patients with refractory ascites also have Type 2 hepatorenal syndrome (HRS) defined as a gradual decline in renal function with a serum creatinine >133μmoL/L and no other apparent cause for renal dysfunction. Patients with Type 2 HRS are predisposed to developing the more serious Type 1 HRS which is defined as a doubling of serum creatinine to > 221μmoL/L in less than two weeks (8). The other criteria for the diagnosis of HRS include severe cirrhosis, failure of volume expansion to improve renal function, and the absence of a secondary cause for renal dysfunction (nephrotoxic agents, shock, bacterial infection) or proteinuria (<500 mg/dL) (8).

Renal dysfunction in cirrhosis is associated with significant morbidity and mortality. The median survival of a patient with refractory ascites and Type 2 HRS is 6 months and Type 1 only 2 weeks. Pre-transplant renal insufficiency is an independent predictor of death and is a risk factor for chronic renal failure post-transplant (10,11). Patients with pre-transplant HRS have longer ICU stays, more complications and higher in-hospital mortality than non-HRS patients (12). Reversal of renal dysfunction pre-transplant reduces post-transplant complications (13).

In summary, there is a spectrum of ascites defined by its response to therapy and the presence or absence of renal dysfunction. All of these stages (diuretic responsive, diuretic refractory, Type 2 HRS, Type 1 HRS) share a common pathogenesis.

1.3 The pathophysiology of ascites and HRS (the peripheral arterial vasodilation hypothesis).

The pathogenesis of circulatory changes and the development of ascites and renal insufficiency in patients with cirrhosis is complex. Although less apparent in the compensated cirrhotic, decompensated cirrhosis is associated with a hyperdynamic circulatory state (increased cardiac output and heart rate, and a reduction in the mean arterial pressure (MAP) and systemic vascular resistance) (14). Systemic and especially splanchnic vasodilation result in a reduction in the effective circulating volume. The vasodilation is attributed to an increase in circulating vasodilators (i.e. nitric oxide, atrial natriuretic peptide, brain natiuretic peptide, prostacyclin, glucagon, endotoxin). In order to maintain systemic perfusion, compensatory mechanisms such as the renin-angiotensin system, endothelin-1, vasopressin and the sympathetic nervous system are activated (15). The compensatory response leads to renal vasoconstriction, impaired renal sodium excretion and subsequently to impaired water excretion. Salt and water retention results in ascites and peripheral edema (16).
Based on this common pathophysiology, current therapies for ascites either focus on symptomatic management (increasing sodium excretion with diuretics or intermittent paracentesis) or on the reduction of portal hypertension via a transjugular intrahepatic potosystemic shunt (TIPS), the use of splanchnic vasoconstrictive agents and liver transplantation). All patients with refractory ascites with or without Type 2 HRS require consideration for transplant.

Unfortunately, waiting times on the transplant list continue to increase and therefore, bridging therapies are required to manage ascites prior to transplant.

1.4 Current therapeutic options for refractory ascites with or without Type 2 HRS and their limitations.

The main bridging therapeutic options for refractory ascites are repeated large volume paracentesis with albumin replacement or TIPS. A recent Cochrane meta-analysis reviewed five randomized trials which compared these 2 approaches (17). Although there was no mortality difference found between the two modalities, TIPS resulted in a higher rate of encephalopathy (odds ratio 2.24, 95% CI 1.39 to 3.6) and a reduced rate of ascites re-accumulation (odds ratio 0.07, 95% CI 0.03 to 0.18). TIPS is associated with other complications including worsened hepatic function, intraperitoneal bleeding (2%), hemolysis (10-15%), sepsis (2-10%) and stent migration (10-20%) (18). The rate of stent occlusion has significantly decreased since the development of coated stents but can still occur (13% versus 44% at 1 year) (19).

The role of TIPS in HRS remains unclear. Although TIPS has been shown to improve Type 2 HRS in some studies, other studies have shown renal dysfunction is an independent predictor of poor outcome post-TIPS (20,21). Newer data suggests that TIPS may have benefit in those patients who respond to combination pharmacologic therapy (midodrine, octreotide, albumin). In a

recent study by Dr. Florence Wong the use of TIPS in five patients who responded to combination therapy (creatinine <133 μmoL/L) resulted in a further improvement in renal function and sodium excretion (22). As not all patients are candidates for TIPS and as both TIPS and large volume paracentesis are associated with adverse events, the search for alternate therapeutic agents is justified.

1.5 The rationale behind using a combination of vasoactive agents and albumin in the treatment of refractory ascites with or without Type 2 HRS.

Multiple pharmacologic agents have been used to improve renal function prior to transplant in patients with Type 1 HRS. These include vasoactive agents such as terlipressin, octreotide and midodrine as well as agents to increase the effective circulating volume such as albumin. Combination therapy has proven to be the most successful in improving renal function in patients with HRS (23). There have been two major trials demonstrating the efficacy of midodrine, octreotide and albumin in patients with Type 1 HRS. In these studies, the mean duration of therapy ranged from 14-20 days. Mean time to renal response was 7-10 days (22,24). A low recurrence rate of HRS after therapy suggests that this may be a partially reversible process (25,26). As the pathophysiology of Type 1 HRS, Type 2 HRS and refractory ascites are all believed to result from peripheral arterial vasodilation, there is rationale to treating refractory ascites with or without Type 2 HRS with combination vasoconstrictor and albumin therapy.

Little information is available on the effects of combination therapy on refractory ascites or Type 2 HRS. Although the serum creatinine may be within normal range in some of these patients, refractory ascites is associated with a reduction in renal perfusion. As demonstrated by Gadano *et al.*, renal perfusion can be improved in these patients with vasoactive agents (27).

As patients with refractory ascites are increasingly managed as outpatients, the ideal therapeutic agent would be one that would not require admission to hospital. Terlipressin, vasopressin, somatostatin, noradrenaline, dopamine and other infusions therefore would not be practical for this purpose. The available data on the agents most amenable to outpatient care (midodrine, octreotide) and albumin in the setting of refractory ascites with or without Type 2 HRS is presented below.

1.5.1 Midodrine is an oral alpha adrenergic agonist that increases systemic and splanchnic pressures. This increases effective circulating blood volume and thereby improves renal perfusion (28). In a study of non-azotemic cirrhotic patients, the administration of 15 mg of midodrine resulted in an increase in the systemic vascular resistance, suppression of aldosterone and improvement in the renal plasma flow, inulin GFR and sodium excretion during the 6 hours following drug administration. The lack of improvement in those parameters with concurrent HRS was attributed to the impaired vasoconstrictor responsiveness in the sicker group of patients (28). In a second study, midodrine 10 mg po tid was administered for 7 days to 39 non-azotemic cirrhotic patients with and without ascites. A significant increase in urine sodium excretion and

systemic vascular resistance were seen in both groups. In the group with ascites, an increase in the GFR and a decrease in the plasma renin activity and aldosterone were also seen (29).

1.5.2 Octreotide is a long acting analog of somatostatin, has a selective splanchnic vasoconstrictive effect, reduces portal pressures and inhibits the release of renin and aldosterone (30-33). It may also help to overcome the vascular unresponsiveness to vasoconstrictors which has been documented in cirrhotics (34-36). Octreotide (600 µg/day) along with diuretics was given to two patients with refractory ascites in a recent case report. An increase in the MAP, reduction in the heart rate and a reduction in the levels of plasma active renin, plasma aldosterone and glucagon were noted. The glomerular filtration rate (GFR) as measured by the plasma disappearance of Tc99m-DTPA (diethylenetriaminepenta-acetic acid), sodium excretion and ascitic fluid control also improved (37). A second study showed no benefit in systemic hemodynamics or renal function with Octreotide 250 µg sc bid for 5 days but did show a reduction in plasma glucagon, renin activity and aldosterone (30).

Octreotide-LAR is a long-acting formulation containing microspheres of octreotide administered as an intramuscular injection. In a previous study of cirrhotic patients, high concentrations of the drug were still present at one month post-injection suggesting adequate bioavailability with q monthly dosing (38). Octreotide-LAR administered over a 3 month period has also been shown to reduce the portal pressure (as measured by the hepatic venous pressure gradient) in patients with compensated cirrhosis (39). Furthermore, octreotide-

LAR also demonstrated a reduction in circulating vascular endothelial growth factor (VEGF) that the authors speculated may reflect a reduction in portal venous inflow.

1.5.3 Albumin has proven to be effective in restoring intravascular volume and improving renal function when used in combination with vasoconstrictor therapy (23). The use of 50 grams of albumin per week for anywhere from 4 weeks to 3 years was studied in 14 patients with refractory ascites. There was a significant reduction in body weight and a significant increase in serum albumin levels (40). Even when administered alone, it is suggested that albumin improves urinary sodium excretion and the effectiveness of diuretic therapy (41,42).

1.5.4 The combination of octreotide and midodrine (7.5 mg po tid) versus octreotide (300 μg sc bid) alone administered over an 11 day period has been studied in nonazotemic cirrhotic patients with ascites. A reduction in the GFR (Tc99m-DTPA) was seen in the octreotide only group whereas the combination group had a small benefit on GFR. (43). We can extrapolate from data in a trial done by Ortega *et al.* looking at terlipressin and albumin in HRS administered for a maximum of 15 days (23). Although the data was limited by the small number of Type 2 HRS patients (5/21), there was a trend towards better complete renal response and improved outcomes with combination therapy in Type 2 versus Type 1 HRS. Recurrence at 3 months occurred in only 25% of Type 2 HRS patients.

After reviewing the literature it became apparent that no study had tested a combination of vasoconstrictor + albumin therapy in patients with refractory ascites with or without Type 2 HRS. This was a natural extension from the use of combination therapy in Type 1 HRS as the pathogenesis of both disorders are likely to stem from peripheral arterial vasodilation.

Several other limitations of existing studies were noted. First, it was recognized that current studies in the area of pharmacologic therapy for ascites are limited by their small sample size, short duration and non-randomized study design. Secondly, apart from the albumin study by Trotter *et al.*, the discussed studies have not included patients with refractory ascites (40). As well, octreotide-LAR, a superior choice for a outpatient administration has not been adequately tested in this study population. Furthermore, follow-up after study completion has been limited in most studies and there is no consistent outcome measure utilized in all trials. Therefore it was justified to design a 1 month prospective trial studying the impact of octreotide-LAR, albumin and midodrine in patients with refractory ascites.

Prior to designing such a trial however it was important to identify the most appropriate outcome measures based on the existing literature.

1.6 The limitations of measures of renal dysfunction in cirrhosis and the need to define an appropriate renal outcome measure.

It was recognized that another key limitation of the current literature was the lack of clearly defined renal outcome measures. Choosing an appropriate primary outcome measure is crucial in designing a trial to ensure the results are clinically meaningful. As a multitude of outcome measures are utilized in existing trials, we felt it was important to systematically identify and evaluate outcome measures in all contemporary HRS trials and use this to inform the planned prospective trial as well as other future trials. This was the purpose of the first paper in this thesis (chapter 2), a now published systematic review entitled "Renal and other Clinically Relevant Outcomes in Hepatorenal Syndrome Trials" (44).

Previously used measures of renal function have included serum creatinine, calculated creatinine clearance, measured creatinine clearance, GFR by inulin clearance, radioisotope methods and the serum cystatin C concentration. The evidence behind each of these measures in cirrhotic patients is outlined below:

- **Serum creatinine**

  Creatinine is produced by the liver, stored in muscle and excreted by the kidneys. Creatinine is falsely lowered in cirrhotic patients as demonstrated by multiple studies (26,45-48). The mechanism for this reduction is multifactorial, related to a reduction in hepatic synthesis of creatine by 50%, reduced muscle mass, and malnutrition. Tubular secretion of creatinine increases as glomerular filtration wanes, also blunting the increase in serum creatinine. Hyperbilirubinemia can have a site dependent impact on the

creatinine level as measured by the kinetic Jaffe method. In a study by Caregaro *et al.* the sensitivity of serum creatinine, calculated creatinine clearance and measured creatinine clearance were compared to inulin clearance in cirrhotic patients. Sixty-nine percent of patients had ascites and the baseline measured creatinine clearance was 101.3 mL/min. The respective sensitivities to predict a GFR < 80 mL/min compared with renal clearance of inulin were 18.5%, 51% and 74% (47).

- **Calculated creatinine clearance by the Cockcroft-Gault formula**

  The CG formula for GFR in mL/min is: (49)

(140-age *(years)* **x weight** *(kg)***) / (serum creatinine** *(mg/dL)* **x 72)** ** *Modifier: female status (multiply by 0.85)*

Several studies have demonstrated that the Cockcroft-Gault equation overestimates the GFR in cirrhotic patients, especially with renal dysfunction (45,47). Data regarding the change in the accuracy of the CG equation when patients are stratified by stage of decompensation is discrepant. A study by Orlando *et al.* suggested that the CG equation and plasma creatinine overestimated GFR in patients with the most severe rating of hepatic dysfunction (Child's C) but not in the least severe (Child's A) patients (48). The Child score is defined in Appendix one.

- **Calculated creatinine clearance by the Modification of Diet in Renal disease (MDRD) formula**

The abbreviated 4 variable MDRD formula for GFR in mL/min/1.73m2 is expressed as follows: (50,51).

186.3 x serum creatinine$^{-1.154}$ *(mg/dL)* **x age$^{-0.203}$** *(years)* **x 0.742 (if female) x (1.21 if black)**

A cross sectional study by Skluzacek *et al.* compared GFR measurements obtained by the MDRD and Cockroft-Gault equations with renal clearance of iodine 125-labeled iothalamate (125I-iothalamate). Patients were cirrhotic with an average serum creatinine of 1.0 ± 0.1 mg/dL (88 ± 9 μmol/L). Both the MDRD and the Cockroft-Gault equations significantly overestimated GFR (52).

- **Measured 24 hour creatinine clearance**

As a result of tubular secretion of creatinine, as the GFR decreases, measured creatinine clearance results in an overestimation of the true GFR. This overestimation as compared to inulin clearance ranges from 30-80% in several studies. A systematic review of 7 studies demonstrated that the measured creatinine clearance overestimated inulin clearance by a mean of +13 ml/min/1.73 m2. The measured creatinine clearance performed worse at a lower GFR (27). Overestimation is greater in patients with a lower inulin clearance level (53).

- **GFR by inulin clearance (Cln)**

  The inulin based GFR is considered the gold standard for evaluation of renal function. For practical purposes, it is limited to clinical research because of its technical challenges and cost (12).

- **Serum cystatin C concentration**

  Cystatin C is a cationic protein produced by all nucleated cells at a constant rate. Although it is filtered by the glomerulus, unlike creatinine, it is not secreted by the renal tubule. As cystatin C has a constant rate of synthesis, lack of degradation and lack of tubular secretion, it is proposed to be a better measure of renal dysfunction than serum creatinine. A study in cirrhotic patients compared serum creatinine and serum cystatin C to the accepted gold standard, inulin, for detection of a reduced GFR. The sensitivity of cystatin C for detection of a GFR of < 90 ml/min was 85.7% as compared to 28.5% for serum creatinine (54). A second study compared serum cystatin C and measured creatinine clearance with 99mTc-DTPA clearance in 26 patients with cirrhosis. Pearson's correlation analysis revealed a significant correlation between serum cystatin C and 99mTc-DTPA but not with serum creatinine or measured creatinine clearance (55). A study by Orlando *et al.* compared patients with decompensated cirrhosis to controls. The sensitivity of 1/cystatin C had a sensitivity of 88% for detecting an inulin GFR of <72 mL/min. Serum creatinine had a sensitivity of 23% and 12 hour measured

creatinine clearance had a sensitivity of 81%. The plasma cystatin C concentration was not altered by the degree of hepatic decompensation (56).

- **Radioisotope methods**

  The clearance of 99mTc-DTPA (diethylenetriaminepenta-acetic acid) and 125I-iothalamate are alternate methods to estimate GFR. They have not been adequately tested in the cirrhotic population.

In summary, there are multiple techniques for measuring renal function. In cirrhotic patients, each technique has inherent limitations ranging from poor sensitivity (serum creatinine) to impracticality (inulin clearance). In this situation it was useful to survey the existing literature for any consensus regarding the most commonly utilized technique (Chapter 2).

1.7 Study hypothesis

Refractory ascites with or without Type 2 HRS are mediated in part by diminished circulatory volume and that treatment with midodrine, octreotide and albumin may improve renal function, naturesis and paracentesis-adjusted body weight by restoring effective circulating volume and systemic perfusion. The diference in the paracentesis-adjusted body weight was calculated by subtracting the adjusted end of study weight (end of study weight + paracentesis weight in the month on treatment) from the adjusted baseline study weight (baseline study weight + paracentesis weight in the month preceding the study). The exploration of this hypothesis is the subject of the second paper in this thesis (Chapter 3). The aim of this study is to improve splanchnic hemodynamics, reduce portal

hypertension and improve renal perfusion using a combination of octreotide, midodrine and albumin in patients with refractory ascites or Type 2 HRS. The results of this study will extend observations from studies in Type 1 HRS by examining the effects of combination therapy in patients at an earlier stage in the progressive renal dysfunction cascade. From evidence discussed above, renal response may be expected to be better than that seen in Type 1 HRS.

The main implications of this research are the potential for preventing, improving or reversing renal dysfunction at an earlier stage in cirrhosis. This would allow for a longer bridge to transplantation. Combination therapy may reduce the number of patients with refractory ascites going on to Type 2 HRS and likewise to Type 1 HRS. Intuitively, this may have a significant impact on pre-transplant survival and overall mortality.

1.8 Bibliography for Chapter 1

(1) D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-231.

(2) Gines P, Quintero E, Arroyo, V. et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987(7):122-128.

(3) Arroyo V, Gines P, Planas R, Panes J, Rodes J. Management of patients with cirrhosis and ascites. Semin Liver Dis 1986;6:353-369.

(4) D'Amico G, Pasta L, Madonia S, Tarantino G, Mancuso A, Malizia G, et al. The incidence of esophageal varices in cirrhosis. Gastroenterology 2001;120:A2.

(5) Bories P, Garcia-Compean D, Michel H, Bourel M, Capron JP, Gauthier A, et al. The treatment of refractory ascites by the LeVeen shunt: a multi-center controlled trial (57 patients). J Hepatol 1986;3:212-218.

(6) Runyon BA. AASLD practice guideline: Management of adult patients with ascites due to cirrhosis. Hepatology 2004;39(3):841-856.

(7) Moore KP, Wong F, Gines, P. et al. The management of ascites in cirrhosis: report of the Consensus Conference of the International Ascites Club. Hepatology 2003;38:258-266.

(8) Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi, G. et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164-176.

(9) Planas R, Montoliu S, Balleste B, Rivera M, Miquel M, Masnou H, et al. Natural history of patient hospitalized for management of cirrhotic ascites. Clin Gastro Hep 2006;4:1385-1395.

(10) Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg, C.L. et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.

(11) Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a non renal organ. NEJM 2003;349:931-940.

(12) Rimolo A, Gavaler JS, Schade RR, El-Lankani S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. Gastro 1987;93:148-156.

(13) Restuccia T, Ortega R, Guevara M, Gines P, Alessandria C, Ozdogan O, et al. Effects of treatment of hepatorenal syndrome before transplantation on post-transplantation outcome. A case control study. J Hep 2004;40:140-146.

(14) Moller S, Hillingso J, Christensen E, Henriksen JH. Arterial hypoxaemia in cirrhosis: fact or fiction? Gut 1998;42:868-874.

(15) Moller S, Henriksen JH. Neurohormonal fluid regulation in chronic liver disease. Scand J Clin Lab Invest 1998;58:361-372.

(16) Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen J, Rodes J. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;5:1151-1157.

(17) Saab S, Nieto JM, Lewis SK, Runyon BS. TIPS versus paracentesis for cirrhotic patients with refractory ascites. Cochrane Collaboration 2006.

(18) Boyer T. AASLD guideline: The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. Hepatology 2005;41:386.

(19) Bureau C, Garcia-Pagan JC, Otal P, Pomier-Layrargues G, Chabbert V, Cortez C, et al. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a randomized study. Gastroenterology 2004;126(2):469-475.

(20) Spahr L, Fenyves D, N'Guyen VV, Roy L, Legault L, Dufresne, M.P. et al. Improvement of hepatorenal syndrome by transjugular intrahepatic portosystemic shunt. Am J Gastroenterol 1995;90:1169-1171.

(21) Schepke M, Roth F, Koch L, Heller J, Rabe C, Brensing, K.A. et al. Prognostic impact of renal impairment and sodium imbalance in patients undergoing transjugular intrahepatic portosystemic shunting for the prevention of variceal rebleeding. Digestion 2003;67:146-153.

(22) Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin and TIPS in selected patients with cirrhosis and Type 1 hepatorenal syndrome. Hepatology 2004;40:55-64.

(23) Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras, D., et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002;36:941-948.

(24) Angeli P, Volpin R, Gerunda, G. Crighero, R., Roner P, Merenda R, Amodio P, et al. Reversal of Type 1 hepatorenal syndrome with the adminsration of midodrine and octreotide. Hepatology 1999;29:1690-1697.

(25) Iwatsuki S, Popovtzer MM, Corman JL, Ishikawa M, Putnam CW, Katz FH, et al. Recovery from hepatorenal syndrome after orthotopic liver transplantation. NEJM 1973;289:1155-1159.

(26) Guevara M, Gines P, Fernandez-Esparrach G, Sort P, Salmeron JM, Wladimiro J, et al. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. Hepatology 1998;27:35-41.

(27) Gadano A, Moreau R, Vachiey F, Soupison T, Yang S, Cailmail S, et al. Naturetic response to the combination of atrial naturetic peptide and terlipressin in patients with cirrhosis and refractory ascites. J Hepatol. 1997;26:1229-1234.

(28) Angeli P, Volpin R, Piovan D, Bortoluzzi A, Craighero R, Bottaro S, et al. Acute effects of the oral administration of midodrine, an alpha-adrenergic agonist on renal hemodynamics and renal function in cirrhotic patients with ascites. Hepatology 1998;28:937-943.

(29) Kalambokis G, Fotopoulos A, Economou M, Pappas K, Tsianos EV. Effects of a 7-day treatment with midodrine in non-azotemic cirrhotic patients with and without ascites. Journal of Hepatology 2007;46:213-221.

(30) Sabat M, Guarner C, Soriano G, Bulbena O, Novella MT, Ortiz J, et al. Effect of subcutaneous administration of octreotide on endogenous vasoactive systems and renal function in cirrhotic patients with ascites. Digestive Diseases and Sciences. 1998;45(10):2184-2189.

(31) Sieber C, Gnadinger M, del Rozo E, Shaw S, Weidmann P. Effect of a new somatostatin analogue (sandostatin) on the renin-aldosterone axis. Clin Endocrinol. 1988;28:25-32.

(32) Pomier-Layrargues G, Paquin SC, Hassoun Z, Lafortune M, Tran A. Octreotide in hepatorenal syndrome. A randomized double-blind, placebo controlled, cross-over study. Hepatology 2003;38:238-243.

(33) Sanyal AJ. Octreotide and its effects on portal circulation. Gastroenterology 2001;120:303-305.

(34) Ryan J, Sudhir K, Jennings G, Ester M, Dudley F. Impaired reactivity of the peripheral vasculature to pressor agents in alcoholic cirrhosis. Gastro 1993;105:1167-1172.

(35) Polio J, Sieber C, Lerner E, Groszmann R. Cardiovascular hyporesponsiveness to norepinephrine, propranolol and nitroglycerin in portal hypertensive and aged rats. Hepatology 1993;18:128-136.

(36) Helmy A, Jalan R, Newby DE, Hayes PC, Webb DJ. Role of angiotensin II in regulation of basal and sympathetically stimulated vascular tone in early and advanced cirrhosis. Gastroenterology 2000;118:565-572.

(37) Kalambokis G, Fotopoulos A, Economou M, Tsianos EV. Octreotide in the treatment of refractory ascites of cirrhosis. Scandinavian Journal of Gastroenterology 2006;41:118-121.

(38) Ottesen LH, Aagaard NK, Kiszka-Kanowitz M, Rehling M, Henriksen JH, Pedersen EB, et al. Effects of a long-acting formulation of octreotide on renal function and renal sodium handling in cirrhotic patients with portal hypertension: a randomized, double-blind, controlled trial. Hepatology 2001;34:471-477.

(39) Spahr L, Giostra E, Frossard JL, Morard I, Mentha G, Hadengue A. A 3-month course of long-acting repeatable octreotide (sandostatin LAR) improves portal hypertension in patients with cirrhosis: a randomized controlled study. Am J Gastroenterol 2007;102:1397-1405.

(40) Trotter J, Pieramici E, Everson GT. Chronic albumin infusions to acheive diuresis in patients with ascites who are not candidates for transjugular intrahepatic portosystemic shunt. Digestive Diseases and Sciences 2005;50(7):1356-1360.

(41) Schindler C, Ramadori G. Albumin substitution improves urinary sodium excretion and diuresis in patients with liver cirrhosis and refractory ascites. J Hepatol 1999;31:1132.

(42) Gentilini P, Casini-Raggi V, Di Fiore G, Romanelli RG, Buzzelli G, Pinzani M, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized controlled trial. J Hepatol 1999;30:639-645.

(43) Kalambokis G, Economou M, Fotopoulos A, Al Bokharhii J, Pappas C, Katsaraki A, et al. The effects of chronic treatment with octreotide versus octreotide plus midodrine on systemic hemodynamics and renal function in nonazotemic cirrhotic patients with ascites. Am J Gastroenterol 2005;100:879-885.

(44) Tandon P, Bain VG, Tsuyuki RT, Klarenbach S. Systematic review: renal and other clinically relevant outcomes in hepatorenal syndrome trials. Aliment Pharmacol Ther 2007;25:1012-1028.

(45) Papadakis MA, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis. Am J Med 1987;82:945-952.

(46) Roy L, Legault L, Pomier-Layrargues G. Glomerular filtration rate measurement in cirrhotic patients with renal failure. Clin Nephrol 1998;50:342.

(47) Caregaro L, Menon F, Angeli, P. et al. Limitations of serum creatinine and creatinine clearance as filtration markers in cirrhosis. Arch Intern Med 1994;154:201-205.

(48) Orlando R, Floreani M, Padrini R, Palatini P. Evaluation of measured and calculated creatinine clearances as glomerular filtration markers in different stages of liver cirrhosis. Clin Nephrol 1999;51:341-347.

(49) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

(50) Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-470.

(51) National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Am J Kidney Dis 2002;39(Suppl 1):S1.

(52) Skluzacke PA, Szewe RG, Nolan CR, Riley DJ, Lee S, Pergola PI. Prediction of GFR in liver transplant candidates. Am J Kidney Dis 2003;42:1169-1176.

(53) Proulx NL, Akbari A, Garg AX, Rostom A, Jaffey J, Clark HD. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. Nephrol Dial Transplant 2005;20:1617-1622.

(54) Woitas P, Stoffel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr HU, et al. Correlation of serum concentrations of cystatin c and creatinine to inulin clearance in liver cirrhosis. Clinical Chemistry 2000;46(5):712-715.

(55) Demirtas S, Bozbas A, Akbay A, Yavuz Y, Karaca L. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. Clinica Chimica Acta 2001;311:81-89.

(56) Orlando R, Mussap M, Plebani M, Piccoli P, DeMartin S, Floreani M, et al. Diagnostic value of plasma Cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. Clinical Chemistry 2002;48(6):850-858.

Chapter 2 - *Systematic review: Renal and other clinically relevant outcomes in hepatorenal syndrome trials*

2.1. Introduction

There are many potential etiologies for renal dysfunction in patients with cirrhosis including hypovolemia, sepsis, administration of nephrotoxic agents, intrinsic renal dysfunction, acute tubular necrosis, and hepatorenal syndrome (HRS). Type 1 and 2 HRS are diagnoses of exclusion with formal diagnostic criteria outlined by the International Ascites Club in 1996 (1). HRS is common in nonazotemic cirrhotic patients with ascites, occurring in 18% by 1 year and 39% at 5 years (2). The median survival of a patient with Type 1 or 2 HRS is reduced to 2 weeks and 6 months respectively (1).

Although the definitive therapy for HRS is liver transplantation, given the poor survival rate of patients with HRS and growing transplant waiting lists, pharmacologic agents have been used in an attempt to improve renal function prior to transplant (3-5). These include vasoactive agents such as terlipressin, octreotide and midodrine as well as agents to increase effective circulating volume such as albumin (6-17). Several studies, including two recent meta-analyses studying the impact of terlipressin on HRS have concluded that treatment may result in improvement in renal function and survival. The impact of study design, comparison of responders and non-responders and consideration of transplantation on these endpoints is unclear (18,19).

Choosing the appropriate primary outcome measure/endpoint is crucial in designing a trial to ensure that the results are clinically meaningful. When considering the proper outcome measures for hepatorenal syndrome trials, three major questions arise. First, what is the existing evidence that treatment leads to an improvement in clinically relevant outcomes such as survival? Second, what is the evidence that renal outcome measures such as serum creatinine are appropriate surrogate outcomes for more clinically relevant endpoints such as mortality, need for renal replacement therapy or bridging to transplant? Third, since renal function is difficult to measure accurately in cirrhotic patients, are such imprecise estimates of renal outcome useful surrogate markers?

In order to assess the appropriateness of currently used outcomes in pharmacologic hepatorenal syndrome trials, it is first necessary to assess what renal and other outcomes are being used. This review will systematically identify and evaluate outcome measures in all contemporary HRS trials in order to inform future trials.

2.2. Methods

2.2.1. Searching

The search was performed with the assistance of a librarian. EMBASE, MEDLINE, Web of Science and the last 180 days of PubMed were electronically searched to identify the renal outcome measures used in hepatorenal syndrome trials using only trials published after the formal definition of HRS was published

in 1996 (1). The reference lists of selected trials were handsearched for missed references.

The following terms: hepatorenal syndrome (and all known synonyms) AND pharmacologic therapy (list of all known pharmacologic therapies for hepatorenal syndrome, synonyms and CAS registry numbers) (Table 2.3).

2.2.2. Selection

Inclusion criteria

Retrospective trials, prospective controlled trials and randomized controlled trials of pharmacologic intervention for the treatment of HRS in adults (>18 years of age) with liver disease and HRS as defined by the International Ascites Club (1).

Exclusion criteria

Non-English articles were excluded. Case reports and case series, studies of renal function pre- and post liver transplantation, those with isolated hepatic hydrothorax, or those studying TIPS (Transjugular Intrahepatic Portosystemic Shunt) or MARS (Molecular Adsorbents Recirculating System) were excluded.

2.2.3. Validity assessment

A quality analysis was carried out by 2 independent reviewers (PT, VGB) using the Jadad scale (20) and other pre-determined quality criteria (reporting of

baseline characteristics, inclusion and exclusion criteria, reporting of excluded subjects,and follow-up >80%).

2.2.4. Data abstraction

The initial comprehensive search and selection of potentially relevant articles was carried out by one reviewer (PT). Data extraction and quality analysis were carried out by 2 independent reviewers (PT, VGB).

2.2.5. Study characteristics and Quantitative data synthesis

Study characteristics, including sample size, type of study, intervention studied and study outcomes were recorded on a standard form. All selected measurements of renal function and other outcomes were recorded if they were reported in the article. An outcome was considered to be a "primary outcome" if so stated in the methods section of the article.

2.3. Results

Of 848 references obtained through our search, 770 were excluded because they were irrelevant or did not meet inclusion criteria. 36 trials were included in the systematic review (figure 2.1).

2.3.1. Quantitative data synthesis (table 2.1)

Of the 36 trials identified, 7 (19%) were randomized controlled trials (7,21-26), 20 (56%) were prospective non-randomized trials (10,11,14,27-43) and 9 (25%)

were retrospective trials(44-52). 58% were available as full text articles. The median number of participants per trial considering all publications was sixteen with a range from three to one hundred and twelve. 50% of studies included only Type 1 HRS patients, 19% included both Type 1 and Type 2 HRS patients and 31% did not distinguish. In the studies including Type 1 and 2 HRS patients, the proportion of Type 2 patients ranged from 7% (49) to 69% (7). One trial included Type 2 HRS patients but did not treat them (52). 69% of trials included either vasopressin or vasopressin analogs (ornipressin, terlipressin) in at least one therapeutic arm. 11% studied octreotide and midodrine therapy and 8% octreotide therapy without vasopressin or vasopressin analogs. 11% studied alternate agents, including furosemide and N-acetylcysteine. After initial plasma volume expansion in all studies, albumin or an alternate volume expander were utilized in 19/36 studies.

2.3.2. Survival outcomes (table 2.2)

Mortality data was available in 32/36 trials. 8 articles expressed mortality data between "responders" and "non-responders", 9 between two treatment groups (or placebo), 13 expressed mortality rates after a non-randomized intervention and 2 compared mortality rates in HRS versus non-HRS patients. Of the nine trials comparing mortality between two treatment groups or placebo, 5 had a randomized controlled design (7,22-25). Three of the full-text articles contained a multivariate analysis (in 99, 21 and 20 patients) (10,43,48) . In 2 of these multivariate analyses, renal response to therapy was an independent predictor of

survival (43,48). 3 of the full-text articles explicitly mentioned censoring for transplanted patients in the survival analysis (10,42,48). 1 study had no transplanted patients and therefore did not require censoring (43). In three of the studies, mortality was mentioned in the context of a primary outcome measure. Sanyal et al. utilized a combined primary endpoint (patient alive on day 14 with creatinine ≤ 1.5 mg/dL on 2 measurements 48 hours apart without relapse of creatinine after the improvement) (23). Two other studies included survival as a separate primary endpoint along with renal function (25,48).

15/36 trials (42%) had information about transplanted patients. 9 expressed transplant rates after a non-randomized intervention, 3 compared rates between responders and non-responders and 3 between two treatment groups (or placebo) (7,10,11).

Two trials compared rates of dialysis (11,49). One compared rates in responders versus non-responders and the other in one treatment group versus the other.

2.3.3. Renal outcomes (table 2.2)

About half (53%) of the papers included used a renal outcome as the primary outcome measure. The three most commonly used renal outcome measures were serum creatinine (100%), urine output (75%) and urine sodium (53%). Creatinine clearance was measured in 47%, and glomerular filtration rate (GFR) by inulin clearance in 11%.

2.3.4. Quality analysis of trials

As insufficient detail was present to complete the quality assessment of abstracts, quality analysis is only reported for full-text articles. The mean Jadad score was 1.3 ± 1.1 out of a possible total score of 5 with three full-text articles scoring >1 (7,25,26). 17/21 trials reported inclusion and exclusion criteria, 19/21 identified relevant baseline characteristics, 17/21 specified the number of excluded patients or had consecutive patient enrollment and19/21 had >80% end of study follow-up.

2.4. Discussion

This systematic review of 36 trials of pharmacologic therapy for HRS highlights the challenges associated with performing research in this area. The majority of trials were limited by small numbers, lack of censoring for transplantation and heterogeneous patient inclusion. Although a mean Jadad score of 1.3 out of 5 is poor, this mostly reflects the fact that the majority of trials were not double-blinded RCT's. Previous meta-analyses of the use of terlipressin in HRS were limited by the assessment of mortality by responder vs. non-responder status (19) and by the combination of a very small number of trials (18).

Mortality is the most robust clinically relevant outcome. Although mortality data was available in most trials, several trial limitations were identified that preclude a definite conclusion. Only 50% of trials explicitly stated that Type 1 HRS patients alone were included. This heterogeneous inclusion of patients limits the

interpretation of results as it is clear from the literature that the natural history of Type 1 and Type 2 HRS is very different (1). Secondly, the comparison of survival between responders and non-responders was a limitation found in 8 trials (22%). Drawing conclusions from comparing responders and non-responders on survival analysis is not advised because non-responder status is determined in part by the likelihood of survival (53-55). For example, those who die early on after treatment is introduced are automatically considered non-responders. As well, some responders to therapy may have improved spontaneously leading to further bias. Thirdly, the median sample size across all trials was only 16 patients. An inadequate sample size increases the potential for Type 2 error (missing an effect that is actually present). Due to the very heterogeneous nature of the mortality analysis in the trials (Table 2), we were unable to combine the data to make firm conclusions about this important endpoint.

Even in the largest placebo controlled trial, there was still no significant difference in transplant-free or overall survival between the placebo and terlipressin groups (23). This is not surprising however, because if a 60 day transplant free mortality rate of 54% is assumed (23), for a trial with 80% power and 95% confidence, the total estimated sample size to detect a 20% reduction in mortality would be 212. To detect a 10% reduction in mortality, 822 patients would be required (MedCalc v9.1.0.1; MedCalc Software, Mariakerke, Belgium). This number of patients

would certainly require a multicenter trial design and would be challenging to complete.

Among the randomized controlled trial data, the best information is obtained from 3 studies (23-25). Both transplant free and overall survival were not significantly different in the study by Sanyal et al. The second study, also in abstract form, compared two vasoconstrictor therapies (administered with albumin) and found no significant difference in survival between the two groups. The third full-text article concluded that 15 day survival was significantly different between the two groups but transplantation or rate of bridging to transplantation was not mentioned. The median survival between the groups differed by ½ day. The other RCTs either had no mortality data or not enough patients to perform a meaningful comparison of groups.

Other clinically relevant outcomes were not consistently captured in HRS trials. The data for renal replacement therapy and hospitalization rates is insufficient to form meaningful conclusions. For patients who are liver transplant candidates, survival to transplantation, in addition to overall survival, is a relevant outcome to assess. If the only benefit of therapy is bridging patients to transplantation, then pharmacologic therapy may not be justified in those patients who are not transplant candidates unless a survival benefit can be demonstrated in these patients. Combined outcomes, as utilized in the study by Sanyal et al. may

reduce the sample size required to demonstrate a significant benefit and should be considered in future trials.

Is there enough evidence that renal outcome measures such as serum creatinine are appropriate surrogate outcomes for more clinically relevant endpoints? An ideal surrogate outcome should be independently and consistently associated with improvements in hard outcomes in well-designed randomized controlled trials (56). A simple correlation with hard endpoints is not sufficient (57). For example, mortality in end-stage cirrhotics may not be related to the hepatorenal syndrome per se, but simply be associated with it because of the presence of a common factor such as advanced hepatic dysfunction (58). The danger of using an inappropriate surrogate outcome is that incorrect conclusions about the impact on hard outcomes may be made. Multiple examples from the literature exist, most notably the effect of encainide and flecanide in arrhythmia suppression (59). As well, although surrogate markers are often easier and faster to obtain, the measurement of multiple unproven variables is limited by cost and by the final utility of the information. When considering the available randomized trials, we do not yet have enough information to support renal outcome measures as valid surrogate outcomes for overall survival.

Lastly, since renal function is challenging to measure in cirrhotic patients, we must also consider the importance of the precision of renal outcome measures in detecting changes in renal function in cirrhosis. Although less data

is available on the utility of urine output and urine sodium as appropriate outcome measures in cirrhotics, there are recognized limitations of other measures (creatinine, creatinine clearance) (14,60-62,62-64). In a study by Caregaro et al., the sensitivity of various estimates of GFR in predominantly decompensated cirrhotic patients were compared to the current gold standard, inulin clearance. The sensitivity to predict a GFR < 80 mL/min compared with renal clearance of inulin was estimated at just 19% for serum creatinine, 51% for the calculated creatinine clearance and 74% for the measured creatinine clearance (60). Inulin glomerular filtration rate, although the gold standard for evaluation of renal function, is limited due to technical challenges and cost (62). Only 11% of all publications in this review measured the inulin clearance. Despite the challenges of diagnosing renal dysfunction in cirrhotics, if less accurate measures of renal function have a consistent association to hard outcomes in future randomized controlled trials, there may not be a need to perform expensive and laborious techniques such as inulin clearance. Given the extremely low sensitivity of serum creatinine however, use of at least the measured creatinine clearance is suggested in future trials.

There are a few limitations to our review that should be considered. First, as with any systematic review, our findings are limited by the availability of published reviews. Although publication bias may affect the reporting of neutral or negative study results, it may have less impact on a review of outcome measures in HRS trials, as in our review. Secondly, although we did use a very

broad search strategy assisted by a librarian, technical limitations prevented us from having 2 reviewers select the studies for inclusion. We did, however, use an informal process for obtaining consensus for study inclusion.

2.5. Conclusions

Hepatorenal syndrome is a challenging area of study in part because of the high mortality rates and its relatively low prevalence. Although a multicenter RCT has recently been completed, the benefit of vasoconstrictor therapy in non-transplant candidates, the impact of pharmacologic therapy on hard outcomes and the validation of renal function measures as surrogates for mortality remains unclear. Lack of a validated surrogate marker makes is difficult to assess new therapies without resorting to sufficiently large multicenter trials such that hard endpoints can be evaluated in each trial, which is clearly impractical. Future trials would benefit from a more homogeneous patient population (ie distinguishing HRS type 1 from type 2), a randomized controlled trial design, adequate power, censoring for transplantation and avoidance of the misleading comparison of responders to non-responders. To achieve the required sample size, consideration should be given to the assessment of combined outcomes (mortality, rate of transplantation, need for dialysis, discharge from hospital) or the initiation of an international HRS database where individual patient data can be pooled and standardized outcomes assessed. Lastly, it is well recognized that renal function is challenging to estimate in cirrhotic patients. At present, we

would suggest that measures of renal function not be used as the sole primary endpoint in future trials.

2.6. Tables and Figures

Figure 2.1.: Trial Flow

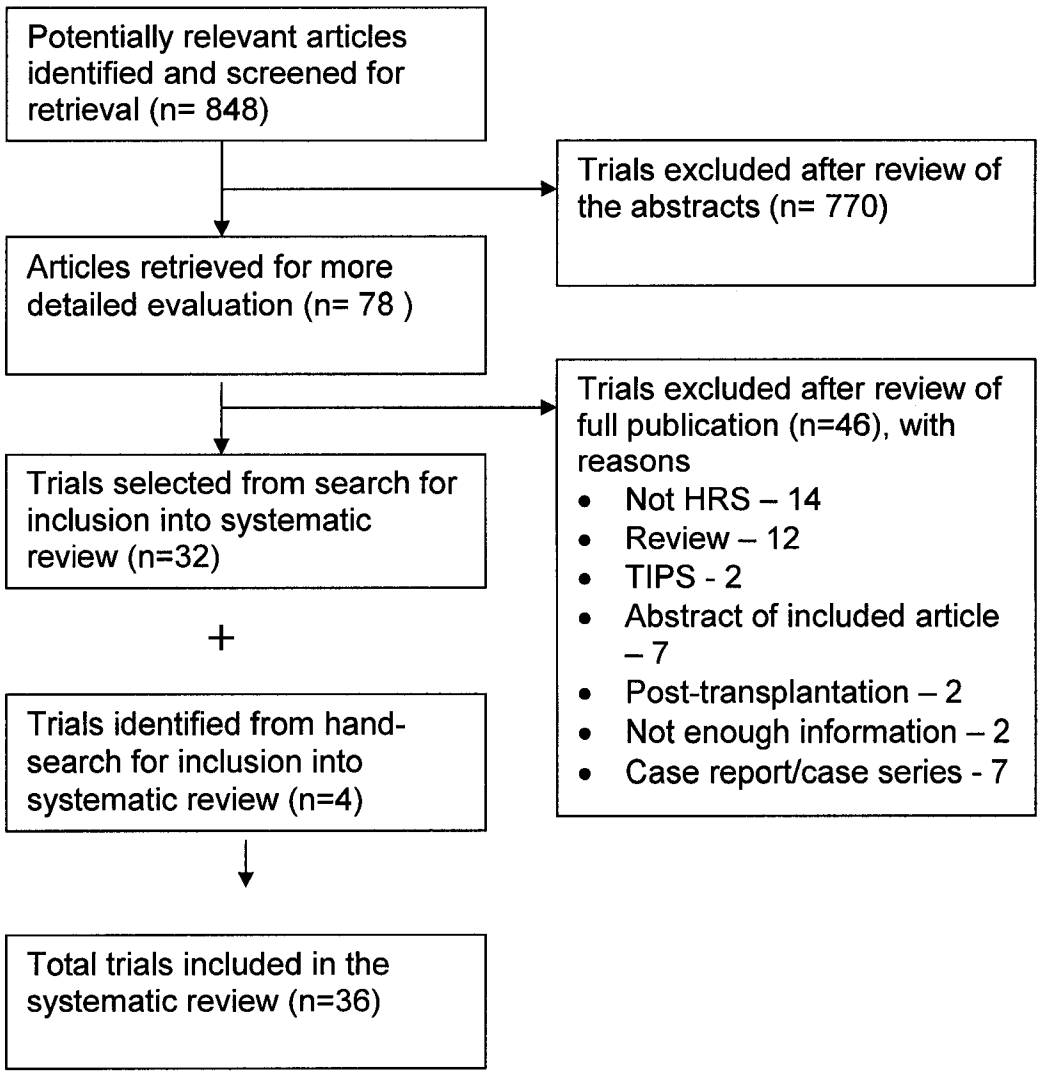


Table 2.1. Trial demographics

Characteristics of studies	N (%) or median ± range
Sample size	16 (3 – 112)
Trial design	
- RCT	7 (19%)
- Prospective non-randomized	20 (56%)
- Retrospective	9 (25%)
Full-text	21 (58%)
Therapy	
-Terlipressin, ornipressin,	25 (69%)
vasopressin	4 (11%)
-Octreotide, midodrine	3 (8%)
-Octreotide	4 (11%)
-Other	
HRS	
-Type 1 alone	18 (50%)
-Type 1 and 2	7 (19%)
-Not distinguished	11 (31%)

Table 2.2. Renal and clinically relevant outcomes

Author, year of publication	Renal outcomes (* for primary)	Clinically relevant outcomes
Jarcuska, P 2002(27) Abstract	Cr, UNa, UO	Mortality[S] *(3/10 died during hospitalization)*
Popescu A, 2004 (21) Abstract	Cr, Cr Cl, UO, UNa	Mortality[AvsB] *(Survival rate in the endothelin-a receptor antagonist group (ET-RA) + terlipressin group was 66% compared to 50% in the terlipressin alone group)*
Gow PJ 2004 (45) Abstract	*Fall in Cr to <0.15 mmol/L or a fall of 20% from the pre-treatment level	Mortality[S] *30/47 died by study conclusion, 21/30 died within 30 days* *Survivors were more likely to be younger, have positive renal response to therapy and have a reversible component to their liver disease or to be listed for transplant*
Hassanein TI, 2001 (28) Abstract	Cr, UO, UNa, *Responder defined as Cr Cl > 40 mL/min after treatment	Mortality[S] *28 day survival was 43% (3/7)without liver transplant*
Abulfutuh AR, 2003 (29) Abstract	Cr, UO, UNa,	Not listed
Chelarescu D 2003 (22)	Cr, UO, UNa	Mortality[AvsB] *(1 pt octreotide versus 2 pts*

Abstract		*octreotide/captopril group (within 3 hours from admission) - no p-value)*
Triantos CK 2004 (46) Abstract	Cr, CrCl, UO, UNa	Mortality[HRSvsOther] *HRS: 8/22 (36%) alive at 6 weeks without transplantation* *Non-HRS: 5/16 (31%) alive without transplantation*
Van der Merwe S 1997 (30) Abstract	Cr, UO	Mortality[S] *All patients died except the 1/20 that was transplanted* Transplant[S] 1/20
Gunther R 1999 (31) Abstract	Cr, Cr Cl, UO	Not listed
Schepke, M 2003 (32) Abstract	Cr, Cr Cl *Renal response defined as reduction in Cr by 50% compared to baseline or to <=1.5 mg/dL or increase in Cr Cl to >40 mL/min	Mortaltiy[S] *Estimated survival was 33.3 ± 9.4 weeks*
Copaci, I 2002 (33) Abstract	Cr	Not listed
Laurent G 2001 (34) Abstract	Cr, Cr Cl, UNa, UO *Renal response = Cr Cl > 40 mL/min	Mortality[R vs NR] *1/7 responders was dead at 3 weeks and 6/6 non-responders were dead at a mean of 10 days after inclusion*

Esrailian E 2003 (47) Abstract	Cr *Reduction of Cr to <1.5 mg/dL	Mortality[AvsB] *49% octreotide, midodrine and albumint group versus 67% control group (p<0.05)*
Sanyal, A 2006 (23) Abstract	Cr *Patient alive on day 14 with Cr ≤ 1.5 mg/dL on 2 measurements 48 hours apart without relapse (27% terlipressin, 16% placebo – p=0.059)	Mortality[AvsB] (Overall survival at 60 days *48% terlipressin, 48% placebo)* (Transplant-free survival at 60 days *48% terlipressin and 46% placebo*)
Sharma, P 2006 (24) Abstract	Cr, Cr Cl, UO *Reversal of HRS (50% in each group) Partial response – decrease of ≥ 50% from baseline at day 15	Mortality[AvsB] *(56% survived in the noradrenaline/albumin group and 50% in the terlipressin/albumin group – p=ns)*
Saner, F 2004 (35) FT	Cr, Cr Cl, UO	Mortality[S] *(4/7 alive at 60 day follow-up; no survival analysis or p value)* Transplant[S] *(1/7 patients transplanted)*
Pomier-Layrargues G, 2003 (7) FT	Cr, Cr Cl, UNa *20% reduction in Cr at day 4 compared to baseline	Mortality[AvsB] *(Unclear – cross-over)* Transplant[AvsB] *(Unclear – cross-over)*
Solanki P, 2003 (25) FT	Cr, Cr Cl, UO * Reversal of HRS (Cr <133	Mortality[AvsB] *(All 5 patients surviving to day 15 had reversal of HRS and belonged*

	µmol/L)	*to terlipressin/albumin group; no day 15 survivors in placebo group – p<0.05; transplantation not mentioned)*
Holt S 1999 (36) FT	Cr, Cr Cl, UNa, UO	Mortality[S] *(Survival rate at 1 month 67%, 3 months 58%; included 2 transplanted patients, no p value or survival analysis)* Transplant[S] *(2/12 patients transplanted)*
Moreau R, 2002(48) FT	Cr *Cr <130 umol/L or a decrease of at least 20% by the end of treatment	Mortality[R vs NR, MV] *(Survival analysis in responders versus non-responders – Day 60 survival 18% versus 0% respectively, p <0.0001) Transplanted patients censored on date of transplant) Multivariate analysis – renal response and Child Pugh ≤ 11were independent predictor of survival)* Transplant[RvsNR] *(77% of transplanted patients were responders)*
Angeli P, 1999 (11) FT	Cr, UO, UNa, inulin GFR, PAH RPF	Mortality[AvsB] *(1 month survival significantly better in the midodrine/octreotide/albumin group; p=-0.01; did not mention censoring for transplant)* Transplant[AvsB] *2 patients in the active treatment group and 1*

		in the control arm. Need for RRT^{AvsB}
Kiser TH, 2005 (49) FT	Cr, UO, UNa *Complete renal response (Cr ≤ 1.5 mg/dL) and discontinuation of renal replacement therapy if required Partial renal response (Cr decreases by 50% to a value >1.5mg/dL for patients who did not require RRT	$Mortality^{RvsNR}$ *(28 day survival different by log rank p=0.013, Censoring for transplant not mentioned)* $Transplant^{RvsNR}$ *(23% versus 0%, p=0.005)* Need for RRT and time on RRT^{RvsNR} *(No difference)*
Gulberg V, 1999 (37) FT	Cr, Cr Cl, UNa, UO * Reversal of HRS (2 fold increase of Cr Cl to >40 mL/min)	$Mortality^{RvsNR}$ *(50% of responders and 33% of nonresponders survived; no p value, survival analysis or censoring mentioned)* $Transplant^{RvsNR}$ *(1/4 responders and 1/3 non-responders)*
Kaffy F 1999 (38) FT	Cr, Cr Cl, UO, UNa	$Mortality^{RvsNR}$ *(25% of responders and 0% of non-responders survived; no p value, survival analysis or censoring mentioned)*

Ortega R, 2002 (10) FT	Cr, UO, UNa, inulin GFR, recurrence of HRS * Complete renal response (Cr ≤1.5 mg/dL)	Mortality[R vs NR, MV] *(Complete responders median survival 50 days versus 14 days, p=0.013; transplant patients censored; renal function not predictive on multivariate, Child Pugh and administration of albumin were)* Transplant[A vs B] *(At 3 months, 5/21 had a transplant (all treated with terlipressin and albumin).*
Duvoux C, 2002 (39) FT	Cr, Cr Cl, UNa, UO * Reduction of Cr to <133 µmol/L	.Mortality[S] *(2 month actuarial probability of survival 50% without transplantation)* Transplant[S] *(3/12 patients underwent liver transplant)*
Halimi C, 2002 (50) FT	Cr, UNa, UO *Decrease in Cr of at least 30% from day 0 to day 5	Mortality[S] *(2 patients survived, both had a renal response; no survival analysis or p value)* Transplant[S] *(1 of the survivors had a transplant)*
Uriz J, 2000 (40) FT	Cr, UO, inulin GFR * Reversal of HRS (reduction in Cr < 1.5 mg/dL	Mortality[S] *(6/9 patients died; Only transplanted patients survived)* Transplant[S] *(3/9 patients transplanted)*
Hadengue A,	Cr, Cr Cl, UO	None listed – study period was short (4 days)

1998 (26) FT		
Eisenman A, 1999 (41) FT	Cr, Cr Cl, UO, UNa	Mortality[HRSvsOther] *(Mortality rate 89% in the HRS group and 82% in the congestive heart failure group)*
Guevara M, 1998 (14) FT	Cr, inulin GFR, PAH RPF	Mortality[S] *(15/16 patients died by 30 days; no survival analysis)* Transplant[S]
Mulkay JP, 2001 (42) FT	Cr, Cr Cl, UNa, UO	Mortality[S] *(Patients were censored at the time of transplant – median survival 42 days; 3 month mortality rate 100% for those who were not transplanted)* Transplant[S] *(3/12 patients transplanted)*
Colle, I 2002 (51) FT	Cr, UNa, UO *Decrease in Cr to a value <130 umol/L or a decrease of at least 20% leading to a stable value.	Mortality[S] *(Renal response to therapy predictor of survival on univariate analysis; no censoring for transplant mentioned)* Transplant[S] *(2/18 patients transplanted)*
Peron, JM 2005 (43) FT	Cr, Cr Cl, UO *Renal response = Cr Cl > 40	Mortality [RvsNR and MV] *(Median survival 259 days versus 14 days in whole group, p<0.0005; Actuarial*

	mL/min or Cr < 132 µmol/L	*survival at 1 month 30% in responders and 0% in non-responders (Type 1 only); Renal response and Type 2 HRS independent prognostic indicators of survival; no transplantation to censor for)*
Duhamel, C 2000 (44) FT	Cr	Mortality^{RvsNR} *(33% of responders (unsuitable for liver transplantation) and 100% of non-responders; no p value, survival analysis or censoring mentioned)* Transplant^{S} *(2/12 patients were transplanted).*
Danalioglu A 2003 (52) FT	Cr, UNa, UO *Improvement in renal function defined as a decrease in Cr under the pre-treatment value and an increase in daily UO	Mortality^{AvsB} *(57% of treated (terlipressin/albumin) Type 1 patients and 100% of untreated patients with p<0.05. No censoring for the 1 transplanted case; univariate analysis only)*

Hard outcome classification

$X^{(RvsNR)}$ – Mortality rate compared in responders versus non-responders

$X^{(AvsB)}$ – Mortality rate compared in those who got treatment a versus b

$X^{(S)}$ – Mortality rate in those who all got the same therapy, not divided into responder and nonresponder

$X^{(HRSvsOther)}$ – Mortality rate in those with HRS versus those without

$X^{(MV)}$ – Renal response independent predictor of survival on multivariate analysis

Renal outcomes

Cr – serum creatinine, Cr Cl – creatinine clearance, UNa – urine sodium, UO – urine output, Inulin GFR – inulin glomerular filtration rate, PAH RPF – para-amino-hippurate renal plasma flow

Table 2.3. Search Strategy (1996 – November 2006)

(exp HEPATORENAL SYNDROME/ or hepatorenal.mp. OR hepatorenal insufficiency.mp. OR hepatorenal disease.mp. OR exp Kidney Failure/ or liver renal disease.mp. OR type 1.mp. OR type 2.mp. OR renal.mp. OR kidney failure.mp. or exp Kidney Failure/ OR renal failure.mp. or exp Kidney Failure/ OR creatinine.mp. or exp CREATININE/ or exp CREATININE CLEARANCE/ OR urine sodium.mp. or exp Sodium Urine Level/ OR serum sodium.mp. or exp Sodium Blood Level/ OR exp Kidney Blood Flow/ or exp Inulin/ or exp Inulin Clearance/ or exp Glomerulus Filtration Rate/ or Inulin GFR.mp. OR renal hemodynamic$.mp. or exp Kidney Blood Flow/ OR MDRD.mp.
exp Creatinine Clearance/ or Cockcroft gault.mp. OR cystatin c.mp. or exp Cystatin C/ OR renal scan.mp. or exp Kidney Scintiscanning/ OR radioisotope.mp. or exp RADIOISOTOPE/ OR DTPA.mp.) **AND** (cirrhosis.mp. or exp Liver Cirrhosis/ OR liver disease.mp. or exp Liver Disease/ OR

splanchnic.mp.) **AND** (42794-76-3.rn. OR 3092-17-9.rn. OR exp OCTREOTIDE/ or Octreotide.mp. OR 83150-76-9.rn. OR midodrine.mp. or exp MIDODRINE/ OR albumin.mp. or exp ALBUMIN/ OR 1407-84-7.rn. OR 51-41-2.rn. OR noradrenaline.mp. or exp Noradrenalin/ OR exp VASOPRESSIN/ or vasopressin.mp. OR 11000-17-2.rn. OR 38916-34-6.rn. OR 51110-01-1.rn. OR terlipressin.mp. or exp TERLIPRESSIN/ OR exp DOPAMINE/ or dopamine.mp. OR 51-61-6.rn. OR 62-31-7.rn. OR 51-43-4.rn. OR 55-31-2.rn. OR 6912-68-1.rn. OR adrenaline.mp. or exp Adrenalin/ OR exp Inotropic Agent/ or inotrope.mp. OR vasopressor.mp. or exp Hypertensive Factor/ OR exp gelafundin/ or exp Infusion Fluid/ or gelafundin.mp. OR exp Plasma Substitute/ or plasma protein substitute.mp. OR ornithine.mp. or exp ORNITHINE/ OR hydroxyethylcellulose.mp. or exp HYDROXYETHYLCELLULOSE/ OR ornipressin.mp. or exp ORNIPRESSIN/ OR 3397-23-7.rn. OR vasoconstrictor.mp. or exp Vasoconstrictor Agent/ OR alpha adrenergic receptor stimulating agent.mp. or exp OR Alpha Adrenergic Receptor Stimulating Agent/ OR 39028-45-0.rn.

exp THERAPY/ or exp DRUG THERAPY/ or therapy.mp. OR treatment.mp. OR drug$.mp. or exp DRUG/) **AND** (limit to (humans and english language and yr="1997 - 2006"))

2.7. Bibliography for Chapter 2

(1) Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentili P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164-176.

(2) Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993 Jul;105(1):229-236.

(3) Rimolo A, Gavaler JS, Schade RR, el-Lankani S, Starzl TE, Van Thiel DH. Effects of renal impariment on liver transplantation. Gastro 1987;93:148-156.

(4) Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. Transplantation 1995;59(3):361-365.

(5) Lafayette RA, Pare G, Schmid CH, King AJ, Rohrer RJ, Nasraway SA. Pretransplant renal dysfunction predicts poorer outcome in liver transplantation. 1997;48(3):159-164.

(6) Sabat M, Guarner, C. Soriano, G., Bulbena O, Novella MT, Ortiz J, Ri E, et al. Effect of subcutaneous administration of octreotide on endogenous vasoactive systems and real function in cirrhotic patients with ascites. Dig Dis Sci 1998;43:2184-2189.

(7) Pomier-Layrargues G, Paguin SC, hassoun Z, Lafortune M, Tran A. Octreotide in Hepatorenal syndrome: a randomized, double-blind, placebo-controlled crossover study. Hepatology 2003;38:238-243.

(8) Ryan J, Sudhir K, Jennings G, Ester M, Dudley F. Impaired reactivity of the peripheral vasculature to pressor agents in alcoholic cirrhosis. Gastro 1993;105:1167-1172.

(9) Angeli P, Volpin R, Piovan D, Bortoluzzi A, Craighero R, Bottaro S, et al. Acute effects of the oral administration of midodrine, an alpha-adrenergic agonist, on renal hemodynamics and renal function in cirrhotic patients with ascites. Hepatology 1998 Oct Oct;28(4):937-943.

(10) Ortega R, Gines P, Uriz J, Calahorra B, Cardenas A, De las Heras D, et al. Effects of terlipressin administration with and without albumin in hepatorenal syndrome (HRS). A phase II study. J.Hepatol. 2002 APR;36:15-15.

(11) Angeli P, Volpin R, Gerunda G, Craighero R, Con P, Caregaro L, et al. Reversal of type 1 hepatorenal syndrome (HRS) with the combined administration of midodrine and octreotide. Hepatology 1999;29:1690-1697.

(12) Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004;40(1):55-64.

(13) Iwatsuki S, Popovtzer MM, Corman JL, Ishikawa M, Putmnam CW, Katz FH, et al. Recovery from hepatorenal syndrome after orthotopic liver transplantation. NEJM 1973;289:1155-1159.

(14) Guevara M, Gines P, Fernandez-Esparrach G, Sort P, Salmeron JM, Jimenez W, et al. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. Hepatology 1998 JAN;27(1):35-41.

(15) Gadano A, Moreau R, Vachiery F, Soupison T, Yang S, Cailmail S, et al. Naturetic response to the combination of atrial naturetic peptide and terlipressin in patients with cirrhosis and refractory ascites. J Hepatol 1997;26:1229-1234.

(16) Restuccia T, Ortega R, Guevara M, Gines P, Alessandria C, Ozdogan O, et al. Effects of treatment of hepatorenal syndrome before transplantation on post-transplantation outcome. A case control study. J Hepatol 2004;40:140-146.

(17) Moreau R. Editorial: The growing evidence that renal function should be improved in patients with cirrhosis and hepatorenal syndrome before liver transplantation. Journal of Hepatology 2004;40:159-161.

(18) Gluud LL, Kjaer MS, Taastroem A, Christensen E. Terlipressin for hepatorenal syndrome: A cochrane systematic review. J.Hepatol. 2005 APR;42:81-81.

(19) Fabrizi F, Dixit V, Martin P. Meta-analysis: terlipressin therapy for the hepatorenal syndrome. Aliment.Pharmacol.Ther. 2006 Sep 15;24(6):935-944.

(20) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1-12.

(21) Popescu A, Voiculescu M. Association of a selective endothelin-A receptor antagonist (ET-A RA) could improve the outcome of patients with hepatorenal syndrome (HRS). Journal of Hepatology 2004;40(Suppl 1):71-72.

(22) Chelarescu D, Chelarescu O, Crumpei F, Stratan I. Captopril in low dose associated with octreotide in hepatorenal syndrome: A randomized study. J.Hepatol. 2003 APR;38:56-56.

(23) Sanyal A, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Teuber P. A Prospective, Randomized, Double-Blind Placebo-Controlled Trial of Terlipressin for Type 1 Hepatorenal syndrome (HRS). Hepatology 2006;44(4):694A.

(24) Sharma P, Kumar A, Sharma BC, Sarin SK. Noradrenaline versus terlipressin in the treatment of Type 1 hepatorenal syndrome: a randomized controlled trial. Hepatology 2006;44(4):449A.

(25) Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. J.Gastroenterol.Hepatol. 2003 Feb Feb;18(2):152-156.

(26) Hadengue A, Gadano A, Moreau R, Giostra E, Durand F, Valla D, et al. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. J.Hepatol. 1998;29(4):565-570.

(27) Jarcuska P, Hildebrand T, Bena L, Grejtovska B, Roland R, Veseliny E, et al. Hepatorenal syndrome type 1 in patients with acute alcoholic hepatitis treated with continual terlipressin infusion in combination with albumin plasmaexpansion. J.Hepatol. 2002 APR;36:256-256.

(28) Hassanein TI, Abdeen O, El-Tahawy M, Hart M, Khanna A, Mehta R. Octreotide, midodrine, and albumin, triple therapy is effective in reversing Hepatorenal Syndrome. Hepatology 2001 OCT;34(4):542A-542A.

(29) Abulfutuh AR, Morsy MA, Solyman AM, El Hendawy SM, El Desouky ME, El Hadad SM, et al. Role of therlipressine and octreotide in type I hepatorenal syndrome (HRS). J.Hepatol. 2003 APR;38:52-53.

(30) VanderMerwe S, Nevens F, VanRoey G, Fevery J. Ornipressin and/or misoprostol improve renal disturbances but do not change final outcome of hepatorenal syndrome. Hepatology 1997 OCT;26(4):636-636.

(31) Gunther R, Bastian A, Folsch UR, Schmidt WE. Ornipressin - A promising option for the treatment of hepatorenal syndrome in liver cirrhosis patients. Gastroenterology 1997 APR;112(4):A1276-A1276.

(32) Schepke M, Malayeri H, Heller J, Sauerbruch T. Vasoactive treatment of hepatorenal syndrome type 1 (HRS1) with midodrine, octreotide and albumin. Gastroenterology 2003 APR;124(4):A664-A664.

(33) Copaci I, Voiculescu M, Micu L, Cojocaru L, Constantinescu G. Reversal of type I hepatorenal syndrome (HRS) with therlipressine and octreotide. J.Hepatol. 2002 APR;36:49-49.

(34) Laurent G, Marie PJ, Christophe B, Josephine M, Louis PK, Karl B, et al. Treatment of hepatorenal syndrome with albumin and diuretics tailored to central venous pressure. Hepatology 2001 OCT;34(4):539A-539A.

(35) Saner FH, Kavuk I, Lang H, Biglarnia R, Fruhauf NR, Schafers RF, et al. Terlipressin and gelafundin: Safe therapy of hepatorenal syndrome. Eur.J.Med.Res. 2004 FEB 27;9(2):78-82.

(36) Holt S, Goodier D, Marley R, Patch D, Burroughs A, Fernando B, et al. Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. Lancet 1999;353:294-295.

(37) Gulberg V, Bilzer M, Gerbes AL. Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. Hepatology 1999 Oct Oct;30(4):870-875.

(38) Kaffy F, Borderie C, Chagneau C, Ripault MP, Larzilliere I, Silvain C, et al. Octreotide in the treatment of the hepatorenal syndrome in cirrhotic patients. J.Hepatol. 1999 Jan Jan;30(1):174.

(39) Duvoux C, Zanditenas D, Hezode C, Chauvat A, Monin J-, Roudot-Thoraval F, et al. Effects of noradrenalin and albumin in patients with type 1 hepatorenal syndrome: A pilot study. Hepatology 2002;36(2):374-380.

(40) Uriz J, Gines P, Cardenas A, Sort P, Jimenez W, Salmeron JM, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J.Hepatol. 2000 Jul Jul;33(1):43-48.

(41) Eisenman A, Armali Z, Enat R, Bankir L, Baruch Y. Low-dose vasopressin restores diuresis both in patients with hepatorenal syndrome and in anuric patients with end-stage heart failure. J.Intern.Med. 1999 Aug Aug;246(2):183-190.

(42) Mulkay JP, Louis H, Donckier V, Bourgeois N, Alder M, Deviere J, et al. Long term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome: a pilot study. Acta Gastroenterol.Belg. 2001 JAN-MAR;64(1):15-19.

(43) Peron JM, Bureau C, Gonzalez L, Garcia-Ricard F, de Soyres O, Dupuis E, et al. Treatment of hepatorenal syndrome as defined by the international ascites club by albumin and furosemide infusion according to the central venous pressure: a prospective pilot study. Am.J.Gastroenterol. 2005 Dec Dec;100(12):2702-2707.

(44) Duhamel C, Mauillon J, Berkelmans I, Bourienne A, Tranvouez JL. Hepatorenal syndrome in cirrhotic patients: Terlipressine is a safe and efficient treatment; propranolol and digitalic treatments: Precipitating and preventing factors? [1]. Am.J.Gastroenterol. 2000;95(10):2984-2985.

(45) Gow PJ, Testro AG, Angus PW. Terlipressin therapy for hepatorenal syndrome - which patients should be treated. Hepatology 2004;40(Suppl 1):A1111.

(46) Triantos CK, Samonakis DN, Thalheimer U, Cholongitas E, Senzolo M, Stigliano R, et al. Terlipressin for renal failure in cirrhosis. A single centre review. Hepatology 2004:Abstract #1117.

(47) Esrailian E, Pantangco ER, Kyulo N, Hu KQ, Runyon BA. Octreotide/midodrine therapy significantly improves survival in type 1 hepatorenal syndrome: Analysis of 53 treated patients & 21 controls. Gastroenterology 2003 APR;124(4):A718-A718.

(48) Moreau R, Durand F, Poynard T, Duhamel C, Cervoni J-, Ichai P, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. Gastroenterology 2002;122(4):923-930.

(49) Kiser TH, Fish DN, Obritsch MD, Jung R, MacLaren R, Parikh CR. Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. Nephrol.Dial.Transplant. 2005 Sep Sep;20(9):1813-1820.

(50) Halimi C, Bonnard P, Bernard B, Mathurin P, Mofredj A, di Martino V, et al. Effect of terlipressin (Glypressin (R)) on hepatorenal syndrome in cirrhotic patients: results of a multicentre pilot study. Eur.J.Gastroenterol.Hepatol. 2002 FEB;14(2):153-158.

(51) Colle I, Durand F, Pessione F, Rassiat E, Bernuau J, Barriere E, et al. Clinical course, predictive factors and prognosis in patients with cirrhosis and type 1 hepatorenal syndrome treated with Terlipressin: a retrospective analysis. J.Gastroenterol.Hepatol. 2002 Aug Aug;17(8):882-888.

(52) Danalioglu A, Cakaloglu Y, Karaca C, Aksoy N, Akyuz F, Ozdil S, et al. Terlipressin and albumin combination treatment in hepatorenal syndrome. Hepatogastroenterology 2003 Dec;50(Suppl 2):103-105.

(53) Hess KR, Wong ET, Jaeckie KA, Kyrtisis AP, Levin VA, Prados MD, et al. Response and progression in recurrent malignant glioma. Neuro-Oncology 1999;1:282-288.

(54) Friberg S, Taube A, Sylvester R, Oesterling JE. Analysis and Presentation. Urology 1997;49:54-65.

(55) Torri V, Simon R, Russek-Cohen E, Midthune D, Friedman M. Statistical Model to Determine the Relationship of Response and Survival in Patients with Advanced Ovarian Cancer Treated with Chemotherapy. J Natl Cancer Inst 1992;84:407-414.

(56) Bucher HC, Guyatt GH, Cook DJ, Holbrook A, McAlister FA. Users' Guide to the Medical Literature: XIX. Applying Clinical Trial Results: A. How to Use an Article Measuring the Effect of an Intervention on Surrogate End Points. JAMA 1999;282(8):771-778.

(57) Fleming TR, DeMets D. Surrogate End Points in Clinical Trials. Annals of Internal Medicine 1996;125(7):605-613.

(58) Desai M, Stockbridge N, Temple R. Blood Pressure as an Example of a Biomarker That Functions as a Surrogate. The AAPS Journal 2006;8(1):E146-E152.

(59) The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Mortality and morbidity in patients receiving encainide, flecanide, or placebo. N Engl J Med 1991;324:781-784.

(60) Caregaro L, Menon F, Angeli, P. et al. Limitations of the serum creatinine level and creatinne clearance as filtration markers in cirrhosis. Arch Intern Med 1994:201-205.

(61) Papadakis MA, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis. Am J Med 1987;82:945-952.

(62) Sherman DS, Fish DN, Teitelbaum I. Assessing Renal Function in Cirrhotic Patients: Problems and Pitfalls. American Journal of Kidney Diseases. 2003 Feb;41(2):269-278.

(63) Roy L, Legault L, Pomier-Layrargues G. Glomerular filtration rate measurement in cirrhotic patients with renal failure. Clin Nephrol 1998;50:342-346.

(64) Orlando R, Floreani M, Padrini R, Palatini P. Evaluation of measured and calculated creatinine clearances as glomerular filtration markers in different stages of liver cirrhosis. Clin Nephrol 1999;51:341-347.

(65) Tandon P, Bain VG, Tsuyuki RT, Klarenbach S. Systematic review: renal and other clinically relevant outcomes in hepatorenal syndrome trials. Aliment Pharmacol Ther 2007;25:1012-1028.

Chapter 3 - *The effect of midodrine, octreotide and albumin in patients with refractory ascites.*

3.1. Introduction

Refractory ascites occurs in 5-10% of cirrhotic patients with ascites. As initially defined in 1996 and subsequently revised in 2003, refractory ascites is resistant or intractable to maximal diuretic therapy (1,2). The majority (>90%) of refractory ascites cases are diuretic intractable related to the development of renal insufficiency, electrolyte abnormalities or otherwise idiopathic encephalopathy preventing further up-titration of the dose of diuretics (3). Many patients with refractory ascites also have Type 2 hepatorenal syndrome (HRS) defined as a gradual decline in renal function with a serum creatinine >133μmoL/L and no other apparent cause for renal dysfunction (2). In some patients this can progress to the more severe Type 1 HRS. Pre-transplant renal dysfunction is an independent predictor of death and is a risk factor for chronic renal failure post-liver transplantation (4,5).

The pathogenesis of refractory ascites, Type 2 HRS and Type 1 HRS are all linked by peripheral arterial vasodilation. Here, systemic and especially splanchnic vasodilation result in a reduction in the effective circulating volume. The vasodilation is hypothesized to be secondary to an increase in circulating vasodilators such as nitric oxide. In order to maintain systemic perfusion, compensatory mechanisms (renin-angiotensin system, endothelin-1, vasopressin and the sympathetic nervous system) are activated (6). The compensatory response leads to renal vasoconstriction, impaired renal sodium excretion and

subsequently to impaired water excretion. Salt and water retention results in ascites and peripheral edema (7).

As Refractory ascites is associated with a median survival of only 6 months, liver transplantation remains the only curative therapy. Because the waiting list for transplant remains long, bridging therapies including repeated large volume paracentesis and transjugular intrahepatic porto-systemic shunting (TIPS) are the mainstay of care. Both of these options can be associated with significant limitations as well as a reduction in quality of life (8,9). Large volume paracentesis can be complicated by post-paracentesis circulatory dysfunction, protein loss, and procedure-related bleeding or infection. TIPS can be complicated by hepatic encephalopathy, stent occlusion, worsened hepatic function, intraperitoneal bleeding, hemolysis, sepsis and stent migration (10). Furthermore, not all patients are candidates for either of these therapies.

A variety of pharmacologic agents have been used to improve renal function prior to liver transplant in patients with Type 1 HRS. These include vasoactive agents such as terlipressin, octreotide and midodrine as well as agents to increase the effective circulating volume such as albumin. The pathogenesis of refractory ascites, Type 2 HRS and Type 1 HRS are likely related to peripheral arterial vasodilation, which suggests that administering combination vasoconstrictor and albumin therapy to patients with refractory ascites with or without Type 2 HRS would improve naturesis, ascitic fluid control and renal function. As these subjects are outpatients, the use of octreotide-long acting release (LAR) and midodrine would be considered optimal.

Midodrine is an oral alpha adrenergic agonist that increases systemic and splanchnic pressures, thereby increasing the effective circulating blood volume and renal perfusion (11).

Octreotide-LAR is a long-acting formulation containing microspheres of octreotide administered as an intramuscular injection. In a previous study of cirrhotic patients, high concentrations of the drug were still present at one month post-injection suggesting adequate bioavailability with once monthly dosing (12). Octreotide-LAR has also been shown to reduce the portal pressure (as measured by the hepatic venous pressure gradient) in patients with compensated cirrhosis (13). Furthermore, octreotide-LAR demonstrated a reduction in circulating vascular endothelial growth factor (VEG-F) that the authors speculated may reflect a reduction in portal venous inflow. The overall effect of octreotide has been attributed to direct splanchnic vasoconstrictive effects, indirect vasoconstrictive effects through the inhibition of circulating vasodilator hormones (glucagon) and inhibition of the renin-angiotensin system (14).

Human serum albumin has proven to be effective in restoring intravascular volume and improving renal function when used in combination with vasoconstrictor therapy (15). The use of 50 grams of albumin per week has been studied in 14 patients with refractory ascites. In this study there was a significant reduction in body weight and a significant increase in serum albumin levels (16). Even when administered alone, it is suggested that albumin improves urinary sodium excretion and the effectiveness of diuretic therapy

(17,18). The combination of albumin and vasoconstrictor therapy has been shown to be more efficacious than either treatment alone, therefore both were administered in the current study (15).

The primary objective of the study was to assess the change in the inulin glomerular filtration rate (GFR) from baseline to study end (after one month of therapy with midodrine, octreotide-LAR and albumin) in patients with refractory ascites with or without Type 2 HRS. Secondary objectives were to assess the effect of combination therapy on paracentesis-adjusted body weight and naturesis. Although the difference in paracentesis-adjusted body weight is not a validated outcome measure, it was felt to be clinically relevant. The difference in paracentesis-adjusted body weight was calculated by subtracting the adjusted end of study weight (end of study weight + paracentesis weight in the month on treatment) from the adjusted baseline study weight (baseline study weight + paracentesis weight in the month preceding the study). The effect of therapy on neurohormonal parameters (plasma renin, aldosterone, glucagon) was also studied. Lastly, the correlation of different measures of renal function in cirrhotic patients (serum creatinine, calculated creatinine clearance (Cockcroft Gault and abbreviated Modification of Diet in Renal Disease (MDRD) formulae), 24 hour measured creatinine clearance, serum cystatin C, Tc-99m-DTPA (nuclear medicine) and inulin GFR was examined.

The potential implications of this research are the discovery that combination therapy is effective in preventing, improving or reversing renal dysfunction at an earlier stage in cirrhosis. A positive effect of combination

therapy would allow for a longer bridge to transplantation and potentially reduce the number of patients with refractory ascites going on to Type 2 HRS and likewise to Type 1 HRS. As well, it would serve as a proof of concept that the pathophysiology of refractory ascites, Type 2 HRS and Type 1 HRS are linked.

3.2. Patients and methods

3.2.1. Patients

All patients being treated for refractory ascites at the University of Alberta Hospital in Edmonton were potentially eligible for the study. The inclusion criteria required refractory ascites with or without renal dysfunction. As per the international ascites club guidelines, refractory ascites can be divided into diuretic resistant and diuretic intractable ascites. *Diuretic resistance* was defined as a lack of response to dietary sodium restriction (90 mmol/day sodium diet) and intensive diuretic treatment (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week. *Diuretic intractable* ascites was defined as that which could not be mobilized or prevented because of diuretic-induced complications (*renal insufficiency* (doubling in serum creatinine or increase to > 177 цmoL/L), *electrolyte abnormalities* (hyponatremia to <125 mEq/L or potassium > 5.5 mmol/L or <3.5 mmol/L) or unprecipitated *hepatic encephalopathy*) (1,2). Cirrhosis had to be confirmed by biopsy or by evidence of hepatic dysfunction (elevated bilirubin and INR, low albumin) or portal hypertension, and consistent abdominal imaging. All patients had to have received prior counseling about a 2 gram/day sodium-restricted diet. Exclusion

criteria included age <18 years, > grade 2 hepatic encephalopathy, TIPS, alcohol intake, hepatocellular carcinoma beyond the Milan criteria, gastrointestinal bleeding or bacterial infection within the past 2 weeks. Low dose diuretics were continued as tolerated, provided there was no evidence of HRS (creatinine < 133 μmoL/L),

Potential candidates for the study were identified by practicing hepatologists or attending physicians at the University of Alberta Hospital. Dr. Puneeta Tandon was informed of all potential candidates and subsequently discussed the study with these patients. All patients signed an informed consent document after a thorough explanation of the information sheet and study protocol. Prior to initiation, study approval was obtained from the University of Alberta's local health research ethics board as well as Health Canada.

3.2.2. Study drugs

Study medications consisted of midodrine, octreotide-LAR (20 milligrams) which was supplied by Novartis, and albumin. Midodrine 2.5 mg to 5 mg orally three times was titrated on each subsequent visit aiming for an increase in the systolic blood pressure of 15 mm Hg. The midodrine was reduced or discontinued if systolic blood pressure was greater than 140 mm Hg. After the initial study visit, patients returned to receive 50 grams of intravenous albumin (200 cc of 25%) three times per week for the duration of the study. A deep intramuscular injection of 20 milligrams of octreotide-LAR was administered into the gluteal muscle on day one of the study.

3.2.3. Study design and methods

The study was prospective, non-randomized and uncontrolled. After obtaining informed consent, all patients underwent a 24 hour urine collection for creatinine clearance, urine volume, urine protein and urine sodium. The 24 hour urine sample was collected on an outpatient basis the day prior to the start of the study. Both at day 1 and after one month (end of study), patients were admitted to the clinical investigation unit at the University of Alberta hospital for further investigations. A plastic cannula was placed in each arm for obtaining blood samples and for administering inulin. After collection of blood samples and completion of the inulin clearance test patients were started on the study medications as described above.

Body weight, blood pressure and pulse were also recorded at the three times per week follow-up visits for albumin. At the end of one, two and three months, serum creatinine, liver function and complete blood count were repeated.

3.2.4. Outcome measurements

3.2.4.1. Assessment of renal function

The 24 hour urine collection for creatinine clearance, urine volume, urine protein and urine sodium was collected on an outpatient basis. At the beginning and end of the study, the clearance of radiolabelled diethylenetriaminepentaacetic acid (Tc-99m-DTPA) was measured. Two plasma samples were taken at 60 minutes and 180 minutes post-injection. The Tc-99m-

DTPA GFR was corrected for body surface area. On the same day as the DTPA GFR, patients were brought into the clinical investigation unit at the University of Alberta hospital for an inulin clearance test (19,20). All patients remained supine throughout the measurements with the exception of voiding. For the purposes of promoting urine flow, patients were allowed to drink 100-200 mL of free water per hour (for an average of 4-6 hours). The patient was asked to empty their bladder and urine was collected for the measurement of a "blank" inulin level. A serum "blank" was also collected. As per established protocols, a weight based inulin bolus was administered. The inulin bolus was followed by a continuous inulin infusion. Urine was collected during 2 clearance periods with serum inulin levels collected midway between each period permitting two separate calculations of inulin GFR (19,20). The calculated creatinine clearance was calculated using the abbreviated 4-variable (race, gender, serum creatinine, age) MDRD study equation (21). The original version of the MDRD equation was not used as it contains the variable albumin, serum levels of which would be affected by its administration throughout the study period (22). Calculations were done using an on-line MDRD calculator (http://www.nephron.com/MDRD_GFR.cgi).

3.2.4.2. Assessment of systemic hemodynamics and body weight

Blood pressure (BP) and pulse were measured at the beginning and end of the study and three times per week at scheduled study visits for albumin. Mean arterial pressure (MAP) was calculated using the equation (2 (diastolic BP) + systolic BP / 3). For consistency the vital signs were measured after 15

minutes of rest and prior to the administration of albumin. In all patients body weight was measured on the same clinical investigation unit scale without shoes at the beginning and end of the study. In the three patients who received their albumin infusions at peripheral hospitals outside of Edmonton, interim weights were carried out on a different scale than that used for the baseline and end of study weights. The volume of any paracentesis carried out during the study period was recorded and converted to kilograms (1 liter = 1 kilogram). Paracentesis-adjusted body weight was calculated by subtracting the adjusted end of study weight (end of study weight + paracentesis weight in the month on treatment) from the adjusted baseline study weight (baseline study weight + paracentesis weight in the month preceding the study). Although not a validated measure, the paracentesis-adjusted body weight was felt to represent a clinically relevant outcome.

3.2.4.3. Assessment of neurohormonal markers

Neurohormonal markers were measured at the beginning and end of the study period after 1 hour in a supine position. Plasma renin (Cis Bio coated-tube radioimmunoassay), plasma aldosterone (Coat-a-Count no extraction radioimmunoassay (Diagnostic Products Corp, Los Angeles, CA)), plasma glucagon (glucagon double antibody radioimmunoassay (Diagnostic Products Corp, Los Angeles, CA)) and cystatin C (nephelometric measurement on Dade Behring BNII, Milton Keynes, United Kingdom) were collected and analyzed using our standardized laboratory technique. Complete blood count, serum

electrolytes, serum alanine aminotransferase, bilirubin, albumin, INR were measured weekly using standard laboratory assays. Samples for inulin measurement were frozen at -70° C and subsequently analyzed at the University of Toronto (Dr. Florence Wong) using a well-established technique (20,23).

3.2.5. Statistical analysis and power calculation

Statistical analysis was carried out using SPSS 15. Histograms were graphed to estimate the distribution of all variables. In addition to this, the one-sample Kolmogorov-Smirnov (K-S) test (SPSS Version 15) was utilized to confirm the histogram results. A non-significant 2 tailed K-S value suggests that the variable is normally distributed and therefore parametric tests can be utilized. If variables were normally distributed, they were described using a mean ± standard deviation (SD) and a paired t-test (2-tailed) was used to determine whether there was a significant difference between baseline and midpoint or end of study results. If a variable was not normally distributed, it was described using the median and interquartile range (IQR). For these non-normally distributed variables, the nonparametric Wilcoxon Signed Ranks test for related samples was utilized. The level of significance for rejection of the null hypothesis was determined by the number of comparisons being made as the Bonferroni correction was utilized to account for multiple comparisons. We were unable to utilize the two-way repeated measures ANOVA because of the small number of patients in comparison to the number of parameters being tested. The Cronbach's alpha statistic was used as a measure of reliability to compare the

various methods of renal function to each other. This was followed by factor analysis to determine whether the measures were grouped.

The *a priori* sample size calculation was two-fold. From the literature, if refractory ascites and Type 2 HRS occurred together, the mean GFR (by inulin clearance) and standard deviation as determined by a representative sample of patients in the literature was assumed to be 48.5 ± 6.4 mL/min. By our power calculations, we required 5 of these patients to detect a 20% improvement in GFR with 90% power and a 2 sided alpha of 0.05. It is generally felt by clinicians that a 20% improvement in renal function is clinically significant and has a real possibility to translate into other benefits such as increased diuresis.

If refractory ascites patients are considered without Type 2 HRS, the mean GFR (by inulin clearance) was assumed to be 57.9 ± 6.3 mL/min (24). By our power calculations, we would require four refractory ascites patients to detect a 20% change in GFR with 95% power and 2 sided alpha of 0.05. Target enrollment was increased to 10 in order to account for any patient dropouts from death or loss to follow-up.

3.3. Results

3.3.1. Patient characteristics *(Table 3.1)*

From February 2006 to June 2007, eight patients with refractory ascites were enrolled. All eight patients completed the one month study period. Five patients completed the entire study at our local University clinical investigation

unit. The remaining three patients received albumin infusions at external hospitals but returned to the University hospital for baseline and study end measurements. Baseline characteristics of the patients are presented in Table 3.1. Only one patient had diuretic-resistant ascites. The rest were unable to tolerate higher doses of diuretics due to diuretic induced renal insufficiency in four patients and electrolyte imbalance in three patients. The mean age ± standard deviation was 55 ± 7.3 and 6 patients were male. The etiology of cirrhosis was alcohol related in 4 cases, cryptogenic in 2, hepatitis C in 1 and non-alcoholic fatty liver disease in 1. In a single case, the patient had concurrent hepatocellular carcinoma, within the limits of the Milan criteria (25). All patients were Child Pugh Class B cirrhosis at study entry. The mean Model for End stage Liver Disease score (MELD) at study entry was 12.5 ±.2.8. All variables included in Table 3.1 were normally distributed as evaluated by the K-S Test.

3.3.2. Effect of therapy on renal function *(Table 3.2, Figure 3.1a, Figure 3.1b)*

Although the inulin clearance was our primary outcome measure to judge renal response, the accuracy of this measure was in question at either baseline or study end in 5 of the 8 patients. We would have expected the two estimates of GFR obtained at baseline and study end (two clearance periods), to be very close to each other. In 5/8 patients at least one of the groups of clearance periods varied by more than 20 mL/min. We suspect this was related to urinary retention as a foley catheter was not inserted for the study. Therefore, although

we will report the inulin data, it is not considered accurate enough to draw definitive conclusions from and will not be used to correlate with other measures of renal function.

Using the two-tailed paired t-test to compare before and after measures, there was no significant difference in the inulin GFR (p=0.44), calculated creatinine clearance (MDRD) (p=0.39), calculated creatinine clearance (CG) (p=0.55), measured creatinine clearance (p=0.99) or Tc-99m-DTPA GFR (p=0.91) (Table 3.2 and Figure 3.1.a.). When comparing baseline to end of study serum creatinine values or to month one serum creatinine values, no significant differences were identified. Given the small sample size, to reduce the chance of Type 1 error with multiple unnecessary comparisons, in addition to comparing creatinine at study end to baseline, only the month 1 creatinine (not month 2 or 3) was also compared to the baseline value. Furthermore, complete data for month 2 and month 3 values (for all parameters (MELD score, INR, bilirubin, creatinine, platelet count, white blood cell count, hemoglobin) were only available in 6/8 patients. In this case, the last observation carried forward principle was utilized for the missing data.

Of note, our data on cystatin C was pending at the time of the writing of this manuscript.

3.3.3. Midodrine titration and effect of therapy on systemic hemodynamics *(Figure 3.2a. and Figure 3.2b.)*

When the MAP was compared between baseline and end of study, no significant differences were found (Figure 3.2b). Midodrine was titrated upwards in an attempt to achieve a 15 mm Hg rise systolic blood pressure. The maximum dose of midodrine administered was 37.5 mg per day divided in three doses. This was achieved in 50% of the patients. One patient was able to tolerate only a maximum of 7.5 mg. He had a 25 year history of diabetes mellitus and arterial hypertension. Two other patients received a maximum of 15 and 20 mg. The last patient received 22.5 mg. Although his blood pressure would have allowed further up-titration of the dose, on two occasions he presented with otherwise idiopathic encephalopathy when his dose was transiently increased above this level.

3.3.4. Effect of therapy on body weight and paracentesis-adjusted body weight

In the month before the study, the mean volume of paracentesis was 12.8 liters ± 11.2. The mean volume of paracentesis during the study was 6.3 liters ± 7.8. When compared using a paired t-test, this difference was significant (p=0.02).

As discussed above, In order to account for the volume of fluid taken off by paracentesis (1 liter = 1 kilogram), the difference in the paracentesis adjusted body weight was determined. There was a statistically significant difference in the mean adjusted baseline study weight of 100.26 kg ±19.0 when compared to the adjusted end of study weight of 88.70 kg ±23.7 (p=0.008) . Overall the mean

difference in the paracentesis-adjusted body weight was 8.5 kg ± 6.2 kg. If expressed as a percentage of adjusted baseline weight, the mean weight loss in all patients was 9.4 ± 7.7%.

3.3.5. Effect of therapy on naturesis, serum sodium and diuretic use

(Figure 3.3)

Spot urine samples were performed at study baseline, approximately at 15 days and again at the end of study. When these were compared there was a significant (p=0.02) increase in mean naturesis from baseline (28.9 mmol/L ± 22.1) to study midpoint (71.3 mmol/L ± 43.8). This becomes non-significant at the end of the study (49.8 mmol/L ± 44.1) (Figure 3.3). Similarly, when the 24 hour urine sodium is utilized (only performed at study baseline and study end), there is no difference in sodium excretion (p=0.48) from baseline (53.5 mmol/L ± 89.9) to study end (68.0 mmol/L ± 72.8). If one patient with the highest baseline urine sodium excretion is removed from the analysis, the mean spot urine sodium (22.3 mmol/L ± 12.8 at baseline, 63.6 mmol/L ± 41.1 at midpoint, 45.7 mmol/L ± 46.0 at study end) and 24 hour urine sodium values (22.0 mmol/L ± 12.6 at baseline and 47.6 mmol/L ± 47.9 at study end) correlate more closely with each other. Even with this patient removed from the analysis, the difference between spot urine sodium at baseline and midpoint remains significant.

No significant difference was seen when comparing baseline sodium to end of study sodium results. In those patients on diuretic therapy at the start of the trial (5/8 patients), there was no significant reduction in the dose noted.

3.3.6. Effect of therapy on neurohormonal markers *(Figure 3.4)*

There was a statistically significant reduction in the plasma aldosterone levels at the end of study 946 ± 883.2 pmol/L when compared to baseline 2500± 853.8 pmol/L (p=0.04)

Of note, at the time of the writing of this manuscript data on plasma active renin and glucagon were pending.

3.3.7. Effect of therapy on Child Pugh, MELD score and hepatic function parameters *(Figure 3.5, 3.6, 3.7, 1b., Table 3.3)*

The Child-Pugh scores remained similar through-out the study. All patients were Child Pugh class B at baseline. Two patients ended the study as Child Pugh Class C. The mean Child-Pugh score at baseline was 8.5 ± 0.8 and at study end 8.6 ± 1.1. The albumin levels rose significantly from a mean of 32.1 ± 4.8 g/L to a mean of 45.9 ± 7.4 g/L in keeping with albumin administration (p=0.002), making the end of study Child Pugh score artificially lowered.

The MELD scores and its components (bilirubin, INR, creatinine) are graphically represented in Figures 3.5-3.7 and 3.1b. The means, standard deviations and p-values are found in Table 3.3. As 2 comparisons were made for each of these (baseline to study end and then baseline to month 1), a p=0.025 was considered significant). Both the INR and bilirubin significantly worsened from baseline to study end leading to a significant worsening of the MELD. Interestingly, when the baseline values of these variables (INR, bilirubin, MELD)

were compared to month 1 post study completion, no significant difference was detected.

3.3.8. Effect of therapy on hemoglobin, platelet count and white blood cell count *(Figures 3.8a, 3.8b, 3.9a, 3.9b, 3.10a, 3.10b, Table 3.3))*

When all eight patients were considered, there was a statistically significant reduction in the mean hemoglobin from baseline (101.3 ± 23.5 g/L) to study end (94 ± 19.5 g/L), p=0.03. There was also a significant reduction in the mean platelet count from baseline (117.4 ± 80.6 x 10^9) to study end (91.0 ± 68.5 x 10^9), p=0.03. No significant difference in the white blood cell count was noted from study baseline (4.9 ± 2.9 x 10^9) to study end (4.2 ± 3.4 x 10^9) (p=0.18). When baseline to month 1 values were compared for the hemoglobin, platelet count and white blood cell count no significant changes were identified. As two comparisons were performed (baseline to study end and baseline to month one), once the Bonferroni correction was applied, the change in hemoglobin and platelet count was no longer significant (significant p=0.025).

3.3.9. Correlation of measures of renal function

Reliability analysis using the Cronbach's alpha statistic was used to determine the degree of correlation between different measures of renal function. Cronbach's alpha is a measure of internal consistency between different items attempting to measure the same thing. The Cronbach's alpha for the comparison of the baseline values of the calculated creatinine clearance (by the Cockcroft Gault equation), calculated creatinine clearance (by the MDRD equation), measured creatinine clearance and GFR by the Tc-99m-DTPA was high at 0.82.

When the end values of the 4 measures of renal function were compared, the Cronbach's alpha was 0.81. Both of these suggest excellent internal validity of the measures. A Principal Component Analysis (factor analysis) was performed on the baseline measures to determine whether any measures group together. For the baseline values, all measures clustered together. For the end of study values, the Tc-99m-DTPA clustered apart from the other 3 measures.

3.3.10. Adverse events

A single patient noted two episodes of idiopathic encephalopathy when the midodrine dose was increased above 22.5 mg. Although this can not definitively be attributed to the dose increase, it is an interesting observation. No other adverse events were noted through the study.

3.3.11. Clinical outcomes of the patients in the first 3 months post treatment

Three patients were transplanted 3 weeks, 4.5 months, and 7.5 months after study completion. One patient died of progressive liver dysfunction a month after the study was completed. It was discovered at study end that he was continuing to consume ethanol. One patient was placed back on midodrine 15 mg/day and intermittent albumin infusions because of need for recurrent large volume paracentesis 3-4 months after study completion. He has responded well to this therapy with a reduction in the number of required paracenteses. Another patient previously requiring paracentesis every 2 weeks for 5-8 L has only

needed 1 paracentesis in the 3 month follow-up period. The 7th patient has been getting q 3 weekly paracentesis in the 3 month follow-up period as compared to q 2 weekly. Lastly, one patient has not required any paracentesis in the 3 month follow-up period (although he did not require paracentesis before study entry either).

3.4. Discussion

Although limited in the definitiveness of the conclusions by the lack of a control group, this prospective study of eight patients suggests a benefit of combination vasoconstrictor and albumin therapy in the treatment of refractory ascites. The primary outcome, change in renal function by inulin clearance was not evaluable due to technical difficulties. The secondary outcomes, change in paracentesis-adjusted body weight and naturesis were significantly improved, whereas we were not able to detect any changes in renal function as measured by all techniques. The study is unique in that this combination of agents has not previously been studied in this patient population. The findings add support to the role of systemic and splanchnic vasodilation in the pathogenesis of refractory ascites.

Several interesting points are raised. After adjusting for paracentesis volume, all but one patient lost weight on therapy. This was as high as 22% of pre-study paracentesis weight in one patient. If all patients are considered, the mean volume of paracentesis required when comparing the month on treatment to the month before treatment was reduced by almost 50%. This represents a

clinically significant benefit. As expected, there was a significant increase in naturesis at study midpoint which subsequently decreased by study baseline. These findings are consistent with previous studies demonstrating an increase in urinary sodium excretion with isolated midodrine therapy (11,26), isolated intravenous albumin (17,18) or even isolated subcutaneous octreotide (27). The reduction of naturesis by study end suggests a potential tachyphylaxis to one or more of the medications. The combination of midodrine, octreotide and albumin have been examined in two previous studies of Type 1 HRS (28,29). In the study by Angeli *et al*, midodrine, octreotide and albumin therapy was given for 20 days (28). In that study there was an increase in sodium excretion from baseline to day 5 and then a further increase at day 10. In keeping with our results, the sodium excretion at day 20 did not increase significantly as compared to day 10 (45.6 mEq/day from 44.6 mEq/day) (28) suggesting a plateau effect after 10-14 days of combination therapy. Unlike the study by Angeli et al. however, we did not identify a significant increase in the MAP from baseline to end despite up-titration of the midodrine. The reason for this is unclear but it may have in part been related to the relatively higher baseline MAP in this study population or technique and blood pressure cuff related changes. The clear impact of therapy on the effective circulating volume was demonstrated by the reduction in the mean aldosterone level from baseline to study end.

Despite the reduction in weight, there was no change in renal function as measured by multiple parameters. Although the inclusion criteria allowed the recruitment of patients with Type 2 HRS, all 8 patients had isolated refractory

ascites. In other Type 1 HRS trials, 2/3 of patients improved their renal function with combination midodrine, octreotide and albumin therapy (28,29). Although in the current study patients did not start off with normal renal function (mean measured creatinine clearance 72.8 ± 39.1 mL/min), it may have been easier to demonstrate a beneficial response if the baseline dysfunction had been more marked. As well, had the measurement of the GFR by inulin clearance been more accurate, perhaps subtle changes in renal function would have been detected.

The correlation of the parameters of renal function was strong with no consistent clustering. We were unable to test the correlation of these measures of renal function against the inulin GFR because of inaccuracies in its measurement. Although limited by the small number of patients, these comparisons may have allowed for more clinically meaningful conclusions as to the most accurate measures of renal function.

Thirdly, there was a significant deterioration in hepatic function (bilirubin and INR) and MELD score on therapy. The MELD score went up by a mean of 2.5 points. These results have not been described in the literature previously with midodrine, octreotide and albumin therapy. The most relevant published study to correlate our results with is that by Angeli *et al.* because of the drug therapy utilized and the duration of treatment (28). From the information provided in the Angeli study although the bilirubin (4.3 mg/dL to 6.2 mg/dL) and prothrombin activity (44.4% to 40.6%) trended towards worsened function, the differences were not statistically significant (28). In the current study, the

improvement in hepatic function after withdrawal of therapy is strong evidence that this effect can be attributed to the treatment as opposed to worsening hepatic function over time. There are several possible explanations for the increase in bilirubin and INR in the current study. A possible hypothesis is that splanchnic vasoconstriction resulted in a reduction in portal pressure, a reduction in hepatic perfusion and finally a transient impairment in synthetic and excretory function. The worsened hepatic function can be related to post-TIPS studies where there is a marked reduction in portal venous inflow as a result of a shunt. It is well established that the serum bilirubin increases after TIPS and in fact is an independent predictor of mortality post-TIPS occurring as a result of liver failure (10,30-34). A second explanation is not related to a reduction in portal venous inflow but instead to the effect of α-1-adrenergic agonists on intravascular resistance and hepatic perfusion. An earlier study examining the use of methoxamine (another α-1-adrenergic agonist) in 14 patients demonstrated a reduction in hepatic blood flow with this agent (35). Conversely, a study using an α-1-adrenergic antagonist (prazosin) demonstrated an increase in hepatic blood flow as measured by indocyanine green clearance (36). This suggests the possible hypothesis of hepatic dysfunction secondary to a reduction in hepatic perfusion. An alternate explanation for the elevation in the INR is a malabsorption of Vitamin K as a result of the octreotide, although this is not commonly reported in the literature. The bilirubin was not broken down into direct/indirect during the study and there is a remote chance (although not described in the literature) that hemolysis may have occurred as a result of the

intramuscular injection of octreotide-LAR. This worsening in hepatic function parameters has not been identified previously, likely because of the short duration of the majority of trials. Any future studies proposing longer term combination pharmacologic therapy, however should monitor for worsened hepatic function and attempt to clarify its pathogenesis.

Another result not previously published is the trend to reduction in the hemoglobin and platelet count with therapy. These results improved to baseline after one month post therapy, again suggesting a direct treatment effect. Pancytopenia and thrombocytopenia are listed under the octreotide-LAR product monograph as rare adverse events (<1%). Attributing the pancytopenia to octreotide-LAR is brought into question by a recent randomized controlled trial where 60 patients with cirrhosis and hepatocellular carcinoma received the drug and did not experience significant pancytopenia as compared to control (37). This trend to reduction in counts was clinically insignificant and most likely attributed to hemodilution from albumin administration.

Several study limitations need to be discussed. The major limitations of the study are the lack of a randomized controlled study design and the small number of patients enrolled. Without a control group, changes from baseline to study end attributable to the natural history of the disease cannot be differentiated from treatment effect. Another limitation is the potential for misclassification of patients as having refractory ascites. It is impossible to guarantee that all of the patients maintained a stable sodium intake below 2 grams/day from one month before study entry to study completion. A fluctuation

in the sodium intake would have influenced their paracentesis volumes and paracentesis-adjusted weights. In the absence of evaluable data from the inulin GFR, paracentesis-adjusted body weight became the major secondary outcome measure. Paracentesis-adjusted weight is a clinically relevant endpoint for both patients and physicians and although it is reassuring that patient weights either remained the same (one patient) or decreased, we recognize that patients may even have become more compliant with sodium restriction knowing they were being more carefully observed. In order to obtain more objective data, neurohormones were measured to corroborate the improvement in the effective circulating volume with therapy. The significant reduction in the neurohormonal parameter aldosterone is consistent with a true effect of therapy. Although the ideal situation would have been a randomized controlled trial (RCT) focusing on a harder clinical endpoint, as enrollment for even the eight patients included in this study took sixteen months, an RCT would have required a multi-centre design. Furthermore, as limited data were available in the area, a pilot trial was justified prior to evaluating patients in a randomized format. With regards to sample size, the initial power calculation was based on the test characteristics of the inulin GFR, the accepted gold standard. By our *a priori* power calculations, we only required four refractory ascites patients to detect a 20% change in GFR with 95% power. Unfortunately, the inulin clearance proved to be a technically challenging procedure with inconsistent results in several patients. Therefore this could not be utilized as our primary outcome measure. The other measures of renal function are reported to have reduced reliability as compared to the inulin

clearance and, therefore, this study would have required increased numbers of patients to be adequately powered to detect a difference in renal function. In the ideal setting with consistent results, the inulin GFR would also have been utilized as the gold standard for all other measures of renal function to be compared to as well as for our definition of response. Without a gold standard, no definitive conclusions could be drawn about the most accurate renal measure in our study population.

Although all study variables were normally distributed, given the small number of patients in the study, non-parametric testing was carried out for all comparisons using the Wilcoxon Signed Ranks test analysis. The results did not change qualitatively whether parametric or non-parametric statistical tests were utilized. The most appropriate analysis for the data would have been a repeated measures ANOVA but, we were limited in performing this analysis by our small sample size. As well, given the use of multiple tests of statistical significance on the same data, in order to avoid false positive values due to chance, the Bonferroni correction was utilized. It is recognized that this correction is quite conservative. Despite this, apart from the differences in the mean platelet count and mean hemoglobin values, which were non-significant after the Bonferroni correction, the other comparisons retained the same qualitative p-values.

The study can be criticized for choosing a surrogate outcome measure (renal dysfunction) as opposed to a harder outcome such as death or liver transplantation. When the power calculations are done for a hard outcome such as mortality however, the numbers are unachievable without great expense and

multiple centers. For example, to detect a 25% reduction in mortality with an alpha of 0.05 and a beta of 0.20, 346 patients would be required.

Another study limitation is that it is unclear what dose of albumin, midodrine and octreotide are required to result in natiuresis and weight loss. As this study was a pilot trial, high doses of albumin were utilized to avoid false negative results due to insufficient dose. The applicability of the study to the "real world" would be limited if that much albumin were required to cause naturesis.

3.5. Conclusions

Lastly, the study conclusions cannot be extended to patients with Type 2 HRS as no patients matching this definition were enrolled. It would be expected that as the benefit of combination therapy has been shown in Type 1 HRS, that it may also result in some manner of improvement in patients with Type 2 HRS.

In conclusion, this pilot study of eight patients with refractory ascites supports the efficacy of combination vasoconstrictor and albumin therapy in promoting naturesis and paracentesis adjusted weight loss. Within the limitation of the inaccuracy of our primary outcome measure, no effect was seen on renal function. The study raises the novel observations of worsening hepatic function with combination therapy. Given the non-randomized, uncontrolled nature of the trial, the small sample size and the uncertain doses required for clinical efficacy, prior to widespread application, these observations need to be confirmed in a larger prospective multi-centre randomized trial. Although renal dysfunction is a

key determinant of prognosis in patients with cirrhosis, the use of a more clinically relevant endpoint would be preferable in future trials. An improvement in quality of life or a reduction in hospital visits would be potential endpoints for future trials. If reduction in paracentesis volume or reduction in paracentesis adjusted weight were used as outcomes in future trials, it would be best to conduct an *a priori* survey of experts to determine the minimally clinically relevant reduction in weight. As mentioned above, the sample size required for a mortality end-point is challenging. Future trials should attempt to identify predictors of response to therapy and as well better clarify the long-term impact of treatment. Lastly, future trials should identify whether the increase in bilirubin and INR is reproducible and attempt to clarify the pathogenesis by measurement of indocyanine green clearance, conjugated bilirubin and administration of Vitamin K.

3.6. Tables and Figures

Table 3.1. Baseline clinical characteristics (n=8)

	All (n=8) Mean ± 1 Standard deviation
Age (y)	55 ± 7.3
Male	6 (75%)
Child Pugh score	8.5 ± 0.76
MELD score	12.5 ± 2.8
INR	1.39 ± 0.19
Bilirubin (μmol/L)	35.8 ± 13.98
Albumin (g/L)	32.1 ± 4.8
Serum Na (mmol/L)	131.1 ± 4.6
Serum creatinine (μmol/L)	90.4 ± 24.7
Measured 24 hour creatinine clearance (mL/min)	71.5 ± 36.4
Calculated creatinine clearance (CG) (mL/min)	70.5 ± 24.8
Calculated creatinine clearance (MDRD) (mL/min)	83 ± 31.1
Tc99m-DTPA GFR (mL/min)	71.7 ± 17.7
Inulin GFR (mL/min)	73.8 ± 23.6
Hemoglobin (g/L)	101.3 ± 23.5
Platelets (x 10^6)	117.38 ± 80.6
Paracentesis adjusted weight (kg)	100.3 ± 19.0
Mean arterial pressure	82.5 ± 11.9
Etiology of liver disease • **Etoh** • **Hep C** • **Cryptogenic/NAFLD**	 • 4 • 1 • 3
Dose of spironolactone at baseline	87.5 ± 102.6
Dose of lasix at baseline	52.5 ± 63.2

Table 3.2. Effect of therapy on renal function (baseline and study end). Results are reported as mean ± 1 standard deviation

	Baseline	Study end	P value
CCrCl* (MDRD) (mL/min)	83.0 ± 31.1	89.3 ± 30.8	0.39
CCrCl* (CG) (mL/min)	70.5 ± 24.8	73.5 ± 24.2	0.55
Measured CrCl (mL/min)	72.8 ± 39.1	72.7 ± 28.4	0.99
Inulin GFR (mL/min)	73.9 ± 23.6	83.6 ± 37.5	0.44
Tc-99m-DTPA GFR (mL/min)	71.7 ± 17.7	72.4 ± 12.3	0.91
Serum creatinine (μmol/L)	90.4 ± 24.8	84.1 ± 24.7	0.35

*CCrCl =Calculated creatinine clearance

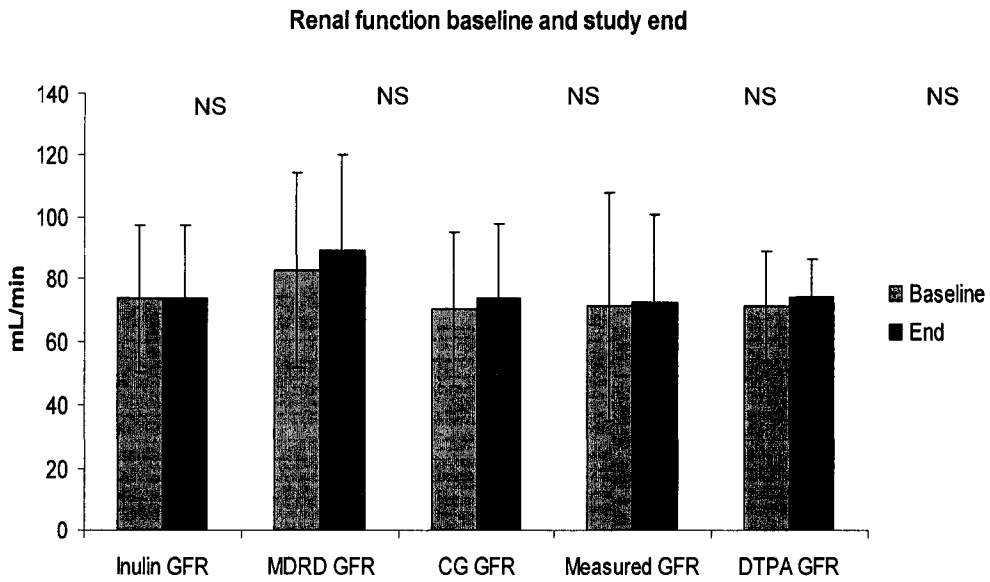
.

Table 3.3. Effect of therapy on hematologic and hepatic function parameters (mean ± standard deviation)

	Baseline	End of treatment	Month 1 post-treatment	Month 2 post-treatment	Month 3 post-treatment
MELD	12.5 ± 2.8	15.4 ± 3.3*	12.5± 3.1	13.0 ± 2.7	14 ± 2.9
Bilirubin (µmol/L)	35.8 ± 14.0	59.8 ± 22.0*	31.8 ± 11.8	38.0 ± 16.6	40.6 ± 17.7
Creatinine (µmol/L)	90.4 ± 24.7	84.1 ± 24.7	85.5 ± 19.7	90.5 ± 26.8	90.6 ± 22.1
INR	1.4 ± 0.2	1.7 ± 0.3*	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.3
Albumin (g/L)	32.1 ± 4.8	45.9 ± 7.4*	31.9 ± 5.6	30.8 ± 6.4	30.0 ± 7.4
Hemoglobin (g/L)	101.3 ± 23.5	94 ± 19.5	105.8 ± 22.1	107.5 ± 23.3	108.8 ± 24.6
Platelets (x 10(9)	117.4 ± 80.6	91 ± 68.5	98.1 ± 41.1	94.6 ± 41.8	94.3 ± 41.8
WBC (x 10(9)	4.9 ± 2.9	4.2 ± 3.4	5.2 ± 3.7	5.1 ± 3.9	5.0 ± 3.9

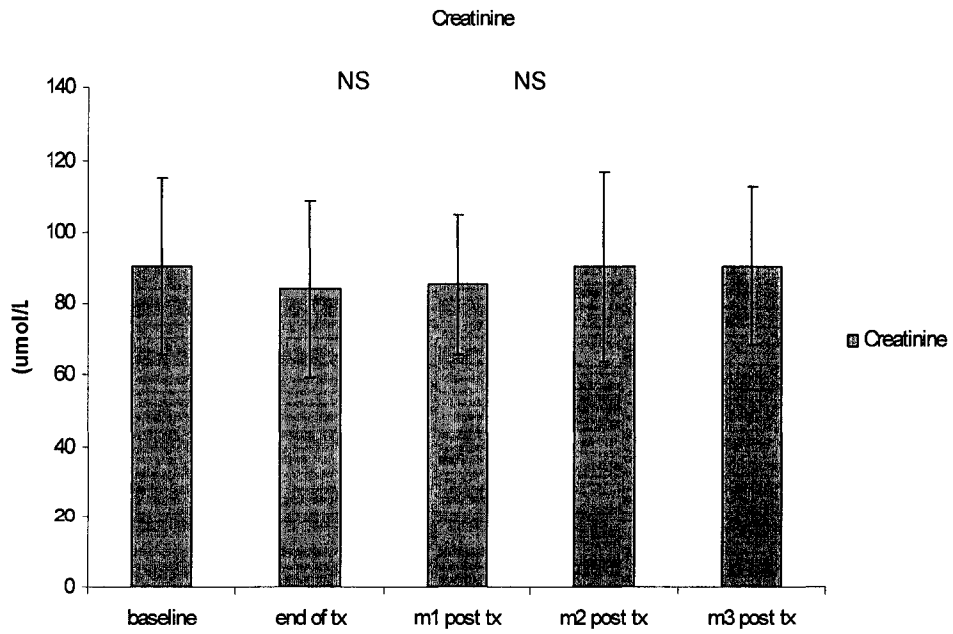
*p value <0.025 as compared to baseline values by the paired t-test (comparisons only made between baseline and end of treatment and then baseline and month 1 post-treatment). Data on month 2 and 3 included for completeness but no comparisons made.

Figure 3.1a. Renal function at baseline and study end (n=8)



-all end of study values are compared by the paired t-test to the baseline values

Figure 3.1b. Mean serum creatinine over time (n=8)



- end of treatment and month 1 post treatment values compared to baselin

Figure 3.2a. MAP over time in individual patients

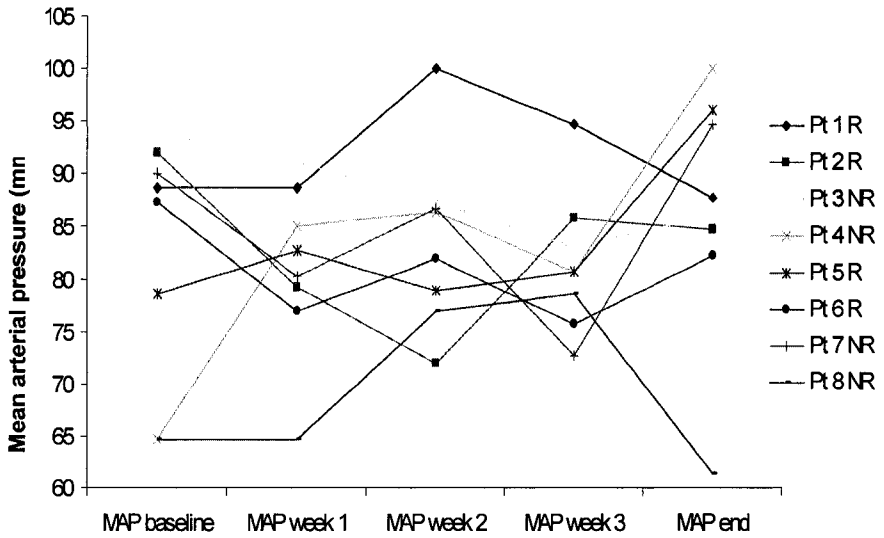
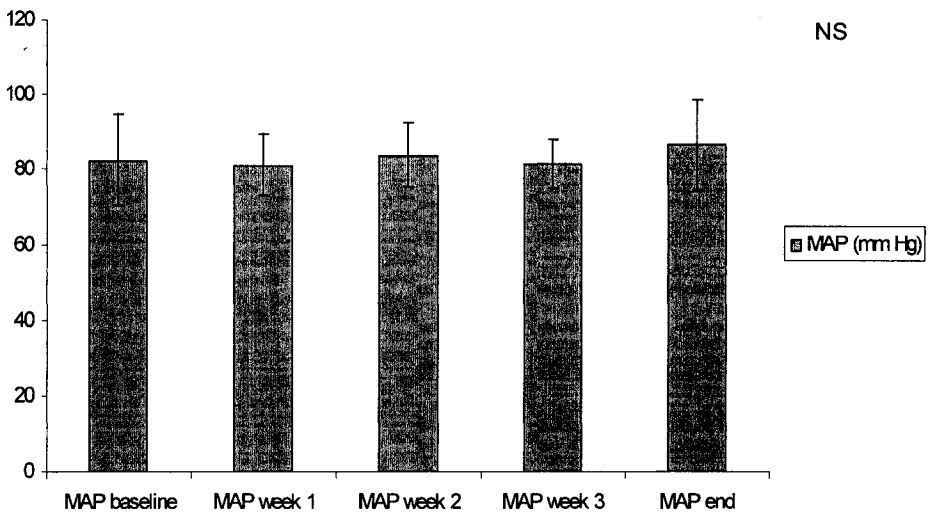
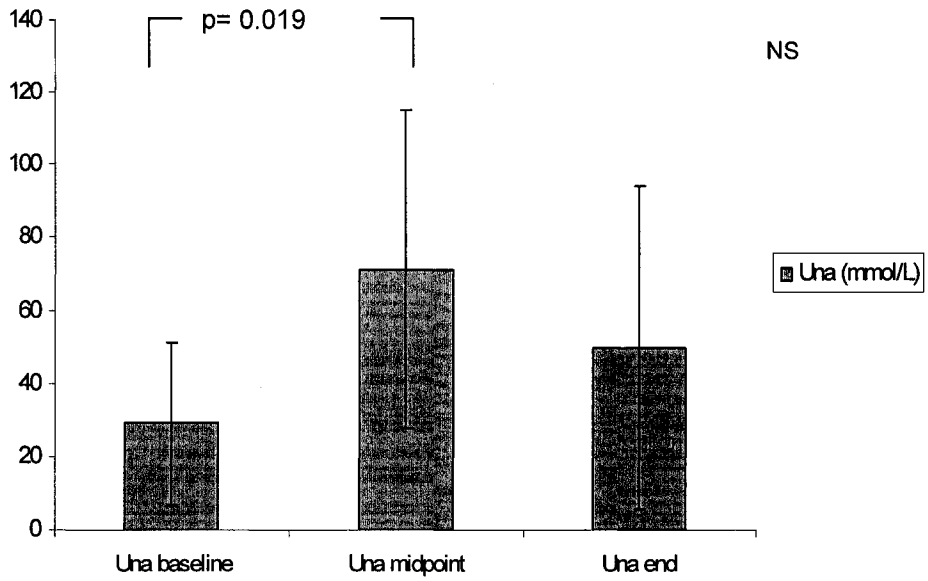


Figure 3.2b. MAP over time (n=8)



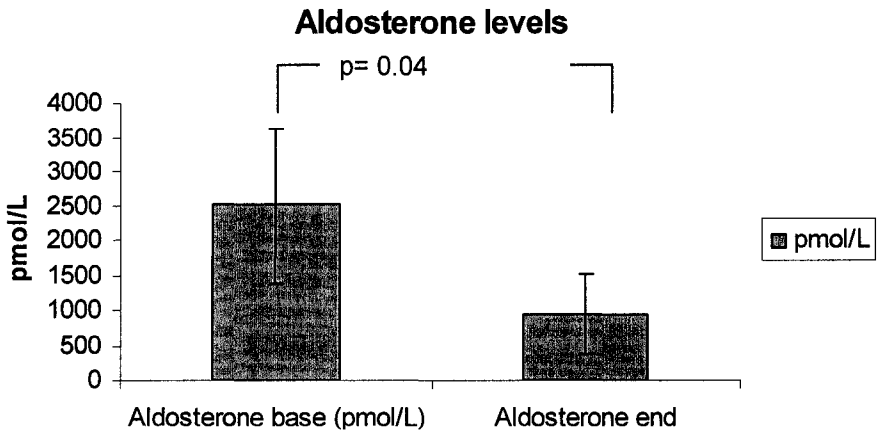
-baseline and study end values compared by the paired t-test

Figure 3.3. Mean sodium excretion (n=8)



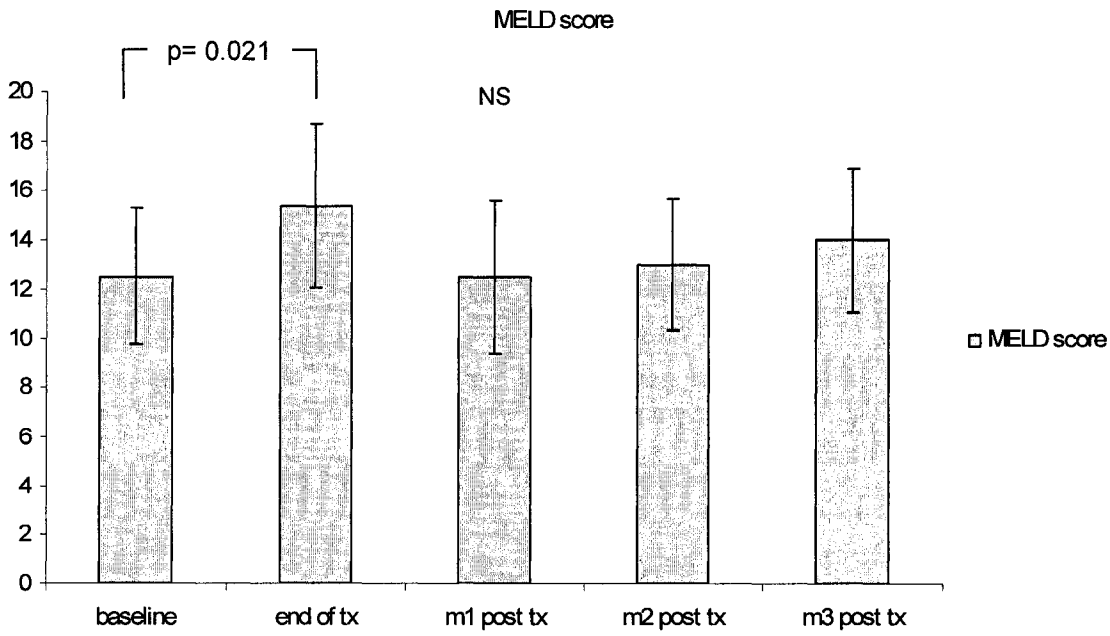
-all values are compared by the paired t-test to the baseline sodium excretion

Figure 3.4. Effect of therapy on aldosterone levels (n=8)



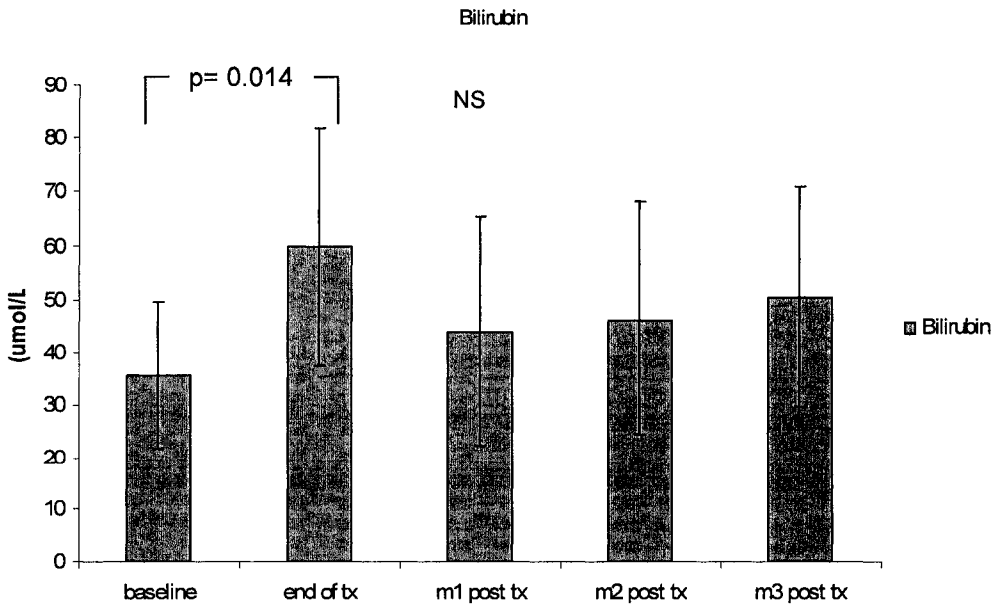
-end of study value compared by the paired t-test to the baseline aldosterone level

Figure 3.5. Mean MELD score over time (n=8)



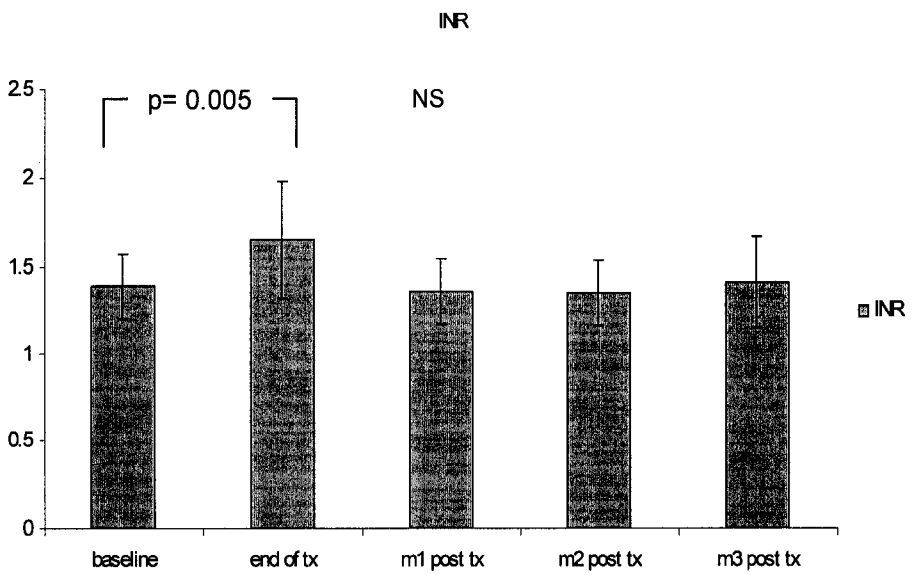
-m1= month 1; tx=study treatment
-end of treatment and month 1 post treatment values compared to baseline

Figure 3.6. Mean bilirubin over time (n=8)



--end of treatment and month 1 post treatment values compared to baseline

Figure 3.7. Mean INR over time (n=8)



--end of treatment and month 1 post treatment values compared to baseline

Figure 3.8a. Effect of therapy on platelet count in individual patients (n=8)

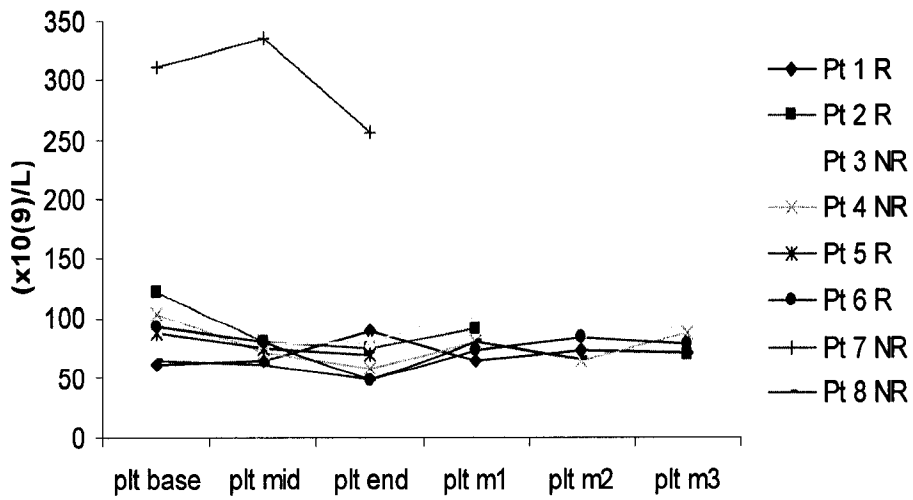
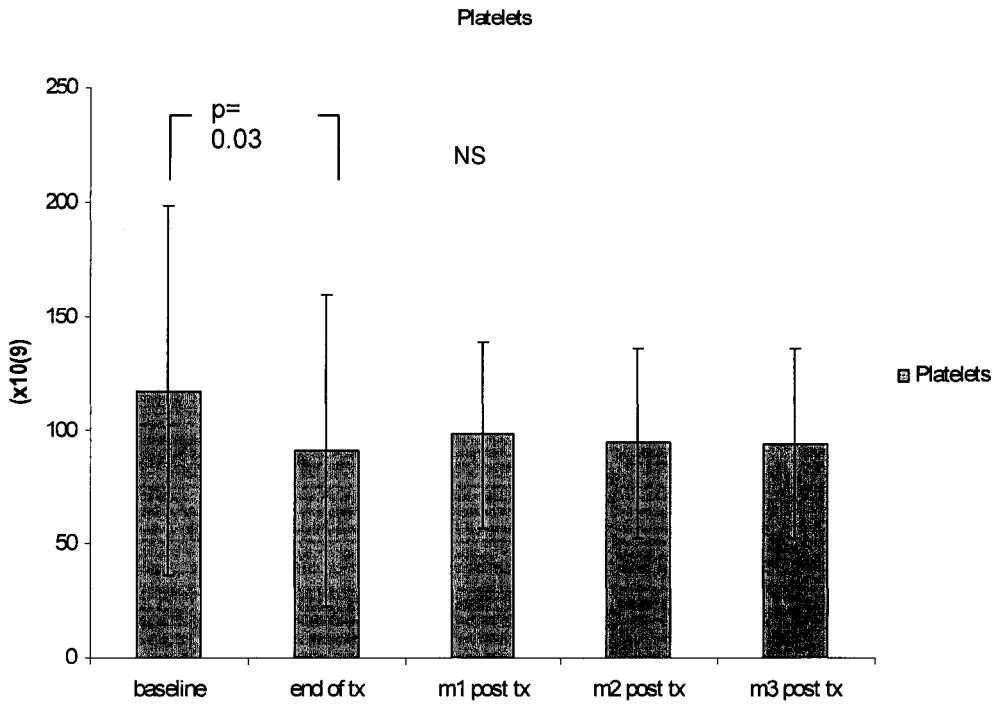


Figure 3.8b. Mean platelet (plt) count over time (n=8)



--end of treatment and month 1 post treatment values compared to baseline

Figure 3.9a. Effect of therapy on hemoglobin in individual patients (n=8)

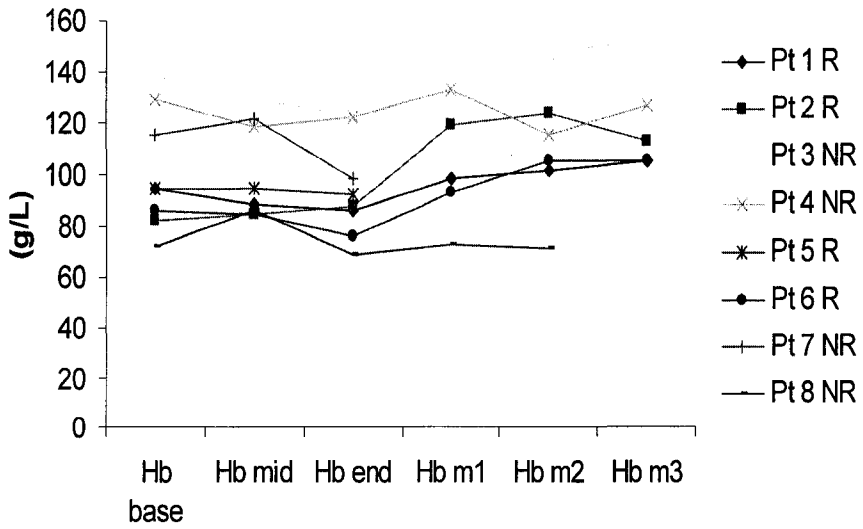
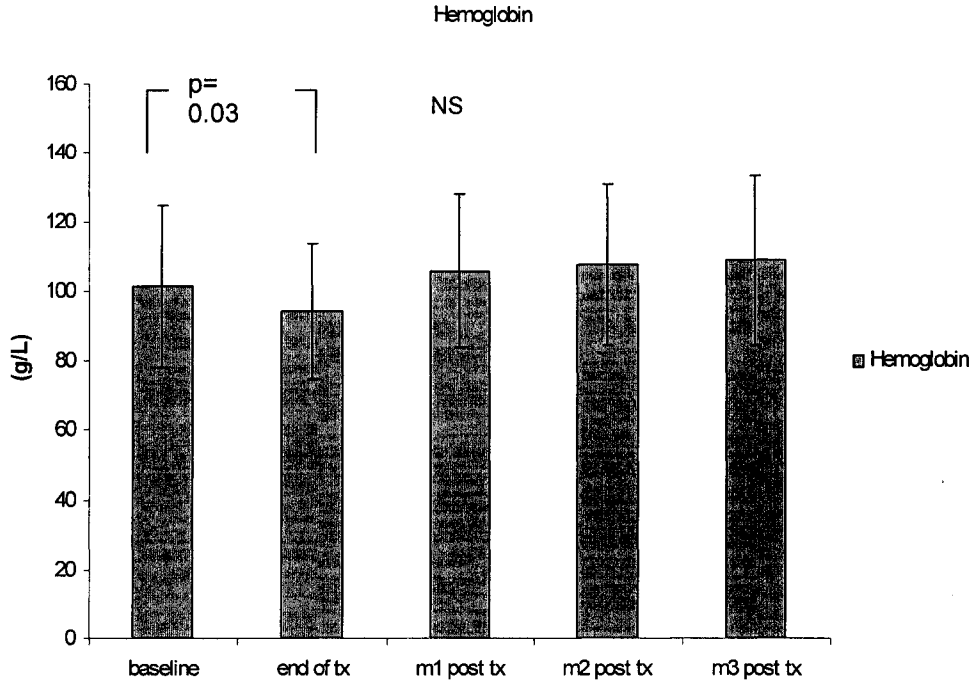


Figure 3.9b. Mean hemoglobin (Hb) over time (n=8)



--end of treatment and month 1 post treatment values compared to baseline

Figure 3.10a. Effect of therapy on white blood cell count (WBC) in individual patients (n=8)

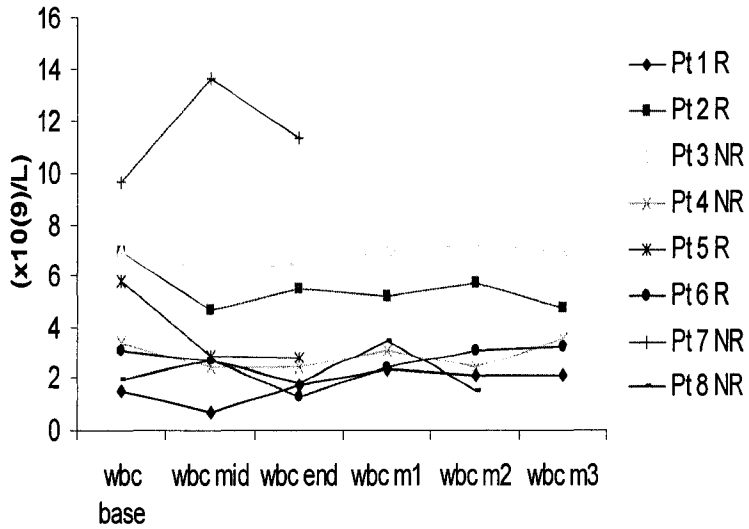
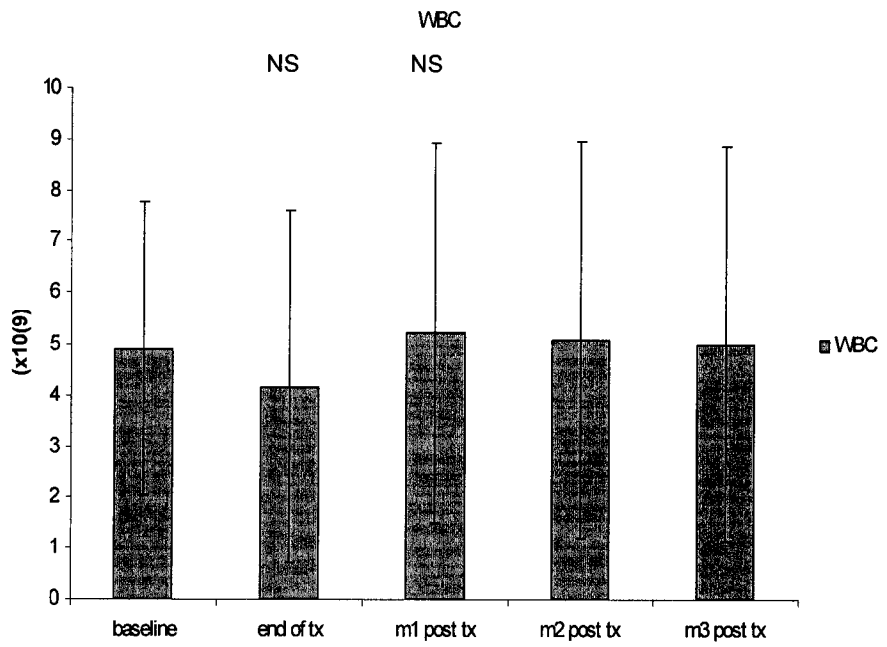


Figure 3.10b. Mean white blood cell count (WBC) over time (n=8)



--end of treatment and month 1 post treatment values compared to baseline

3.7. Bibliography for Chapter 3

(1) Moore KP, Wong F, Gines, P. et al. The management of ascites in cirrhosis: report of the Consensus Conference of the International Ascites Club. Hepatology 2003;38:258-266.

(2) Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi, G. et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164-176.

(3) Planas R, Montoliu S, Balleste B, Rivera M, Miquel M, Masnou H, et al. Natural history of patient hospitalized for management of cirrhotic ascites. Clin Gastro Hep 2006;4:1385-1395.

(4) Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg, C.L. et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.

(5) Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a non renal organ. NEJM 2003;349:931-940.

(6) Moller S, Henriksen JH. Neurohormonal fluid regulation in chronic liver disease. Scand J Clin Lab Invest 1998;58:361-372.

(7) Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen J, Rodes J. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;5:1151-1157.

(8) Saab S, Nieto JM, Lewis SK, Runyon BS. TIPS versus paracentesis for cirrhotic patients with refractory ascites. Cochrane Collaboration 2006.

(9) Campbell MS, Brensinger CM, Sanyal AJ, Gennings C, Wong F, Kowdley KV, et al. Quality of life in refractory ascites: transjugular intrahepatic portal-systemic shunting versus medical therapy. Hepatology 2005;42:635-640.

(10) Boyer T. AASLD guideline: The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. Hepatology 2005;41:386.

(11) Angeli P, Volpin R, Piovan D, Bortoluzzi A, Craighero R, Bottaro S, et al. Acute effects of the oral administration of midodrine, an alpha-adrenergic agonist on renal hemodynamics and renal function in cirrhotic patients with ascites. Hepatology 1998;28:937-943.

(12) Ottesen LH, Aagaard NK, Kiszka-Kanowitz M, Rehling M, Henriksen JH, Pedersen EB, et al. Effects of a long-acting formulation of octreotide on renal function and renal sodium handling in cirrhotic patients with portal hypertension: a randomized, double-blind, controlled trial. Hepatology 2001;34:471-477.

(13) Spahr L, Giostra E, Frossard JL, Morard I, Mentha G, Hadengue A. A 3-month course of long-acting repeatable octreotide (sandostatin LAR) improves portal hypertension in patients with cirrhosis: a randomized controlled study. Am J Gastroenterol 2007;102:1397-1405.

(14) Sanyal AJ. Octreotide and its effects on portal circulation. Gastroenterology 2001;120:303-305.

(15) Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras, D., et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002;36:941-948.

(16) Trotter J, Pieramici E, Everson GT. Chronic albumin infusions to acheive diuresis in patients with ascites who are not candidates for transjugular intrahepatic portosystemic shunt. Digestive Diseases and Sciences 2005;50(7):1356-1360.

(17) Schindler C, Ramadori G. Albumin substitution improves urinary sodium excretion and diuresis in patients with liver cirrhosis and refractory ascites. J Hepatol 1999;31:1132.

(18) Gentilini P, Casini-Raggi V, Di Fiore G, Romanelli RG, Buzzelli G, Pinzani M, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized controlled trial. J Hepatol 1999;30:639-645.

(19) Wong F, Sniderman K, Liu P, Allidina Y, Sherman M, Blendis L. Transjugular intrahepatic portosystemic stent shunt: effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites. Ann Intern Med 1995;122(11):816-822.

(20) Wong F, Liu P, Blendis LM. The mechanism of improved sodium homeostasis of low-dose losartan in pre-ascitic cirrhosis. Hepatology 2002;35:1449-1458.

(21) National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Am J Kidney Dis 2002;39(Suppl 1):S1.

(22) Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-470.

(23) Walser M, Davidson DG, Orloff J. The renal clearance of alkali-stable inulin. J Clin Invest. 1955;34:1520-1523.

(24) Martinet JP, Fenyves D, Legault L, Roy L, Dufresne MP, Spahr L, et al. Treatment of Refractory Ascites Using Transjugular Intrahepatic Portosystemic Shunt (TIPS). Digestive Diseases and Sciences 1997;42(1):161-166.

(25) Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693-699.

(26) Kalambokis G, Fotopoulos A, Economou M, Pappas K, Tsianos EV. Effects of a 7-day treatment with midodrine in non-azotemic cirrhotic patients with and without ascites. Journal of Hepatology 2007;46:213-221.

(27) Kalambokis G, Fotopoulos A, Economou M, Tsianos EV. Octreotide in the treatment of refractory ascites of cirrhosis. Scandinavian Journal of Gastroenterology 2006;41:118-121.

(28) Angeli P, Volpin R, Gerunda, G. Crighero, R., Roner P, Merenda R, Amodio P, et al. Reversal of Type 1 hepatorenal syndrome with the adminsration of midodrine and octreotide. Hepatology 1999;29:1690-1697.

(29) Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin and TIPS in selected patients with cirrhosis and Type 1 hepatorenal syndrome. Hepatology 2004;40:55-64.

(30) Gines P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Ruiz Del Arbol, L. et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123:1839-1847.

(31) Rossle M, Ochs A, Gulberg V, Siegerstetter V, Holl J, Deibert, P. et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701-1707.

(32) Gerbes, A.L. and Gulberg, V. Benefit of TIPS for patients with refractory or recidivant ascites: serum bilirbuin may make the difference. Hepatology 2005;41(1):217.

(33) D'Amico G, Luca M, Morabito A, Miraglia R, D'Amico M. Uncovered transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis. Gastroeterology 2005;4:1282-1293.

(34) Deltenre P, Lebrec D, Mathurin P. Uncovered transjugular intrahepatic portosystemic shunt for refractory ascites. Gastroenterology 2006;130(4):1372-1373.

(35) Mastai R, Bosch J, Navasa, M. et al. Effects of alpha-adrenergic stimulation and beta-adrenergic blockade on azygos blood flow and splanchnic haemodynamics in patients with cirrhosis. Journal of Hepatology 1987;4(1):71-79.

(36) Albillos A, Lledo JL, Rossi, I. et al. Continuous prazosin administration in cirrhotic patients: effects on portal hemodynamics and on liver and renal function. Gastroenterology 1995;109(4):1257-1265.

(37) Becker G, Allgaier HP, Olschewski M, Zahringer A, Blum HE. Long-Acting Octreotide versus placebo for treatment of advanced HCC: a randomized controlled double-blind study. Hepatology 2007;45:9-15.

Chapter 4 – *Conclusions*

4.1 Summary of Research

Ascites is refractory in 5-10% of cirrhotic patients. It is hypothesized to occur in a continuum of severity from diuretic-responsive ascites to refractory ascites and then to Type 2 and Type 1 HRS. The pathogenesis of these entities is linked through peripheral vasodilation. Based on this common pathophysiology, pharmacologic therapies combining vasoconstrictor agents with plasma volume expansion have been successful in the management of Type 1 HRS.

Current therapeutic options for refractory ascites consist of repeated large volume paracentesis and TIPS. In addition to the potential for significant adverse events associated with these treatments, not all patients are candidates for TIPS. Therefore, a prospective study was designed with the goals of attempting to identify new therapeutic options for this disorder and demonstrate that refractory ascites with or without Type 2 HRS are part of the spectrum of the same pathophysiology as Type 1 HRS.

Prior to planning the study, we sought to determine the most appropriate outcome measure through a systematic review of the literature. With the assumption that individuals with renal dysfunction would be recruited and with the knowledge that the majority of trials in the area had been done in Type 1 HRS patients, the available studies of Type 1 or Type 2 HRS were synthesized. Thirty-six articles with relevant renal and other clinical endpoints were identified. From this systematic review we determined that the minority of identified studies

were randomized controlled trials (19%). As well, serum creatinine, urine output and urine sodium were the most common renal outcome measures, despite their clear limitations as sensitive measures of renal function. Many studies were flawed by the inclusion of heterogeneous patient populations, lack of power and the limited use of clinically relevant outcomes such as survival, liver transplantation or hospitalization. Only 42% of articles even defined a primary renal endpoint.

Armed with this information, a prospective trial of pharmacologic therapy for refractory ascites with or without Type 2 HRS patients was designed. Due to the relative rarity of the condition, time constraints and lack of funding it was realized that trial design around a "hard" outcome such as mortality would not be feasible. Therefore, in order to maximize study power, the accepted clinical gold standard, the inulin GFR was chosen as the primary endpoint. This was with the recognition that it was a renal outcome measure and with the recognition that a change in this parameter may not correlate with changes in any other clinically relevant outcome measures.

Unlike the majority of trials before this, a sample size calculation was performed. The sample size calculation mandated that at least 4 patients be recruited (refractory ascites only) or 5 patients (both refractory ascites and Type 2 HRS).

From this prospective trial of 8 patients it was determined that combination therapy with midodrine, octreotide-LAR and albumin leads to clinically significant weight reduction and naturesis but may not have any impact on renal function.

The final conclusion could not be definitively proven because of inaccuracy of the primary renal outcome measure. Since we were unable to recruit any patients with Type 2 HRS, the renal function of all of our patients was closer to normal than initially was planned for. The most notable novel observation that arose from this trial was a transient increase in the bilirubin and INR on therapy.

4.2 Implications for Clinical Practice

In the systematic review it was identified that the validity of renal outcome measures as surrogate markers of more clinically relevant endpoints had not yet been established. It was acknowledged that research in this area was challenging because of the low prevalence of the condition. The main implications for clinical practice are that caution should be exercised in interpreting the results of existing studies. The problems identified with drawing conclusions from heterogeneous, underpowered studies that compared responders and non-responders (defined *post-hoc*) were discussed. In addition, the importance of differentiating between surrogate outcome measures such as improvement in renal function and hard outcome measures such as mortality was brought to light.

In our prospective trial it was established that combination therapy does have an impact on paracentesis-adjusted weight reduction and sodium excretion in cirrhotic patients with refractory ascites. Within the limits of the primary outcome measure, no difference in renal function was identified. As this was an uncontrolled pilot study, it was suggested that further trials needed to be done in

the area before midodrine, octreotide and albumin therapy could be accepted as a routine therapeutic alternative for refractory ascites. Furthermore, our study was hypothesis-generating in that we identified a reversible increase in the bilirubin and INR with treatment.

The other major finding of clinical relevance in the prospective study was the practical challenges associated with performance and calculation of the inulin GFR. Although an established protocol was followed very carefully, consistent results were still not obtained. The inconsistency was attributed to incomplete bladder emptying. Future studies using this technique should appreciate this limitation and obtain ethics as well as patient approval for foley catheterization or obtain a bladder scanner to identify whether any residual urine is present in the bladder.

4.3 Implications for future research

The field of refractory ascites and HRS is a very interesting one. Although this research has been able to put into perspective the limitations of existing HRS trials and shows promise in the utilization of midodrine, octreotide and albumin in refractory ascites, there are many other questions that need to be answered.

As discussed in the systematic review, the sample size required to definitively establish that therapies for HRS can decrease mortality is challenging. Large multicentre trials that combine endpoints or focus on other clinically relevant outcomes such as liver transplantation should be performed.

Future trials in the area would benefit from more homogeneous patient inclusion, the use of combined endpoints and multicentre enrollment.

The results of the prospective study need to be confirmed in a large multicentre randomized controlled trial with pre-defined clinically relevant endpoints (improvement in quality of life, reduction in hospital visits, reduction in paracentesis adjusted weight). Dose finding studies need to be performed to determine the minimal effective dose of albumin. Larger studies may allow us to identify predictors of response to therapy. As well, the unexpected observations of increased bilirubin and INR seen in the prospective trial need to be confirmed and investigated. Once the role of combination therapy in refractory ascites with or without Type 2 HRS is clarified, its role in patients with diuretic responsive ascites should also be considered.