Treatment of Hepatorenal Syndrome Octreotide Vs Octreotide Vs Norepinephrine As Part of Triple Therapy

OSMAN M. OSMAN, M.Sc.; FAHIM RAGAB, M.D.; MOHAMED EL-SHAFIE, M.D. and AYMAN MOHARRAM, M.D.

The Department of Critical Care Medicine, El-Galaa Teaching Hospital* and Faculty of Medicine, Cairo University**

Abstract

Aims: The aim was to compare the effectiveness of octreotide versus midodrine versus norepinephrine in the treatment of HRS in a randomized controlled trial.

Methods and Results: Thirty patients were randomized into 3 groups: Group A received 10-15mg TDS oral midodrine, Group B received 50mg subcutaneous octreotide three times daily and Group C received a continuous infusion of Noradrenaline (NA) at an initial dose of 0.5mg/h, designed to achieve an increase in Mean Arterial Pressure (MAP) of at least 10mmHg or an increase in 4-hour urine output to more than 200mL. When one of these goals was not reached, the NA dose was increased every 4 hours in steps of 0.5mg/h, up to the maximum dose of 3mg/h. Only the Noradrenaline group showed a statistically significant increase in creatinine clearance at the end of treatment period. The mean creatinine clearance increased from a baseline of 35.2 ± 7.7ml/min to 59.2 ± 13.8ml/min in the last day of treatment. In the Noradrenaline group, reversal of hepatorenal syndrome was reached in 6 patients out of 10 (60%) with achieved serum creatinine of 1.5mg/dl or less. The goal was achieved after 3 days of treatment in ICU in only 2 patients, the other 4 needed to continue treatment till day 5, in the midodrine group, hepatorenal syndrome was reversed in only 2 patients out of 10 (20%) after 5 days of treatment. In the octreotide group, only 3 patients out of 10 showed reversal of hepatorenal syndrome (30%) after 5 days of treatment.

Conclusion: The use of Noradrenaline combined with albumin remains an effective treatment for HRS. Noradrenaline is the best alternative for Terlipressin as splanchnic vasoconstrictor with almost similar efficacy and safety profile but better as regard the financial cost. The addition of dopamine infusion to Midodrine or octreotide combined with albumin infusion did not result in significant increase in their efficacy, remaining inferior to Noradrenaline.

Key Words: Hepatorenal Syndrome (HRS) – A serious complication of cirrhosis – Is associated with high mortality without treatment.

Conclusion

HEPATO-RENAL Syndrome (HRS) is one of the most detrimental conditions in patients with end stage liver failure. Historically, HRS was considered a terminal disease associated with cirrhosis and was termed “liver-death syndrome”. Furthermore, despite the improved understanding of pathophysiology and the reversibility of renal dysfunction in HRS, mortality remains extremely high especially for type 1 HRS [1]. Precipitants of HRS have been identified; these include bacterial infection, acute alcoholic hepatitis, or bleeding in the upper gastrointesntinal tract. Also iatrogenic precipitants like aggressive use of diuretic medications or the removal of large volumes of ascetic fluid [2].

There are two distinct types of HRS:

Type 1 (HRS): Is characterized by a rapid and progressive impairment of renal function. It is defined as a doubling of the serum creatinine to a level higher than 2.5mg/dL or a 50% reduction of the initial 24-hour creatinine clearance to a level less than 20mL/min in less than 2 weeks.

Type 2 (HRS): It is characterized by a slower and steadier decrease in renal function. This manifests as a rise in serum creatinine to a level greater than 1.5mg/dL. HRS is estimated to occur in 10% of patients hospitalized with cirrhosis and ascites. Approximately 20% of patients with Spontaneous Bacterial Peritonitis (SBP) will develop type 1 HRS, despite rapid resolution of the infection with antibiotics. Fifteen percent of patients undergoing large volume paracentesis (>5L removed) without albumin replacement will also develop type 1 HRS [2]. Without treatment, the median survival time of type 1 HRS is less than 2 weeks. Type 2 HRS carries a slightly better prognosis, with a median survival time of about 6 months [3].
Table (1): Diagnostic criteria of HRS-major and additional criteria.

**Major criteria:**
1. Low glomerular filtration rate, as indicated by serum creatinine greater than 1.5mg/dl or 24 hour creatinine clearance lower than 40ml/min.
2. Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs.
3. No sustained improvement in renal function (decrease in serum creatinine to 1.5mg/dl or less or increase in creatinine clearance to 40ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 liters of a plasma expander.
4. Proteinuria lower than 500mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

**Additional criteria:**
1. Urine volume lower than 500ml/day.
2. Urine sodium lower than 10mmol/l.
3. Urine osmolality greater than plasma osmolality.
4. Urine red blood cells <50 per high power field.
5. Serum sodium concentration lower than 130mmol/l.

All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis but provide supportive evidence [4].

**Pathogenesis:**

The underlying mechanisms are complex, intense renal vasoconstriction is seen as the end result of decreased effective arterial volume and activation of vasoconstrictor systems, despite the presence of ascites and portal hypertension. Coexisting cardiac dysfunction may contribute to the development of HRS [5].

Rationale for the use of vasoconstrictors in patients with HRS is to improve effective arterial blood volume by causing a vasoconstriction of the extremely dilated arterial splanchnic vascular bed. The improvement in the arterial circulatory function leads to a suppression in the activity of vasoconstrictor systems and a subsequent increase in renal perfusion and GFR [6].

Three types of vasoconstrictors have been reported to be effective in HRS: Vasopressin analogues (ornipressin and terlipressin), somatostatin analogue (octreotide) and alpha-adrenergic agonists (noradrenaline and midodrine). In most studies, both drugs have been given in combination with intravenous albumin to further improve the arterial underfilling [7].

**Patients and Methods**

This prospective study was conducted from Feb. 2009 – May 2011. All the HRS was diagnosed by using the major criteria proposed by the international ascites club, namely:

- A low glomerular filtration rate as assessed by serum creatinine level greater than 1.5mg% (132 mmol/L) or creatinine clearance below 40mL/min.
- Absence of shock, ongoing bacterial infection, fluid losses, or treatment with nephrotoxic drugs.
- No sustained improvement of renal function after oral diuretic withdrawal and plasma volume expansion.
- Proteinuria less than 500mg/d and no ultrasonographic evidence of parenchymal renal disease or urinary tract obstruction.

**HRS was defined as a rapidly progressive reduction in renal function based on one of the following criteria:**

- Doubling of the initial serum creatinine level to a level greater than 2-3mg/dl.
- A 50% reduction in the initial 24-hour creatinine clearance level to a level lower than 20mL/min in less than 2 weeks.

**Exclusion criteria were as follow:**

- Improvement in renal function after central blood volume expansion.
- History of infection within the past week.
- Contra indications to noradrenaline (history of coronary disease, obstructive cardiomyopathy, ventricular arrhythmia, or obliterate arterial disease of the lower limbs), and
- A Child-Pugh score greater than 13 (i.e., 14 or 15).

**Study design:**

On suspicion of HRS, patients were transferred to the intensive care unit. A central venous line and urinary bladder catheter were inserted and continuous cardiac monitoring was initiated. Central Venous Pressure (CVP), urine output, and arterial blood pressure (by using a noninvasive technique) were measured every 4 hours. During the preinclusion phase, patients received human albumin infusion (20g/100mL; Laboratories LFB, Les Ulis, France) to maintain CVP above 4mmHg. Thereafter, intravenous boluses of 120mg of furosemide
were infused to maintain CVP below 10mm/hg and urine output above 100mL/4h.

The efficacy of this first line treatment was assessed after 48 hours; failure was defined as daily urine output lower than 600mL and/or lack of improvement in the serum creatinine level or creatinine clearance.

Patients in failure at 48 hours were randomly assigned to one of the following groups:
A- The Midodrine treatment group (n=10).
B- The octreotide treatment group (n=10).
C- The noradrenaline treatment group (n=10).

Treatment strategy:
During all treatments albumin administration (20g/day IV infusion) was pursued to maintain CVP between 4 and 10mmHg. In addition, dopamine infusion at a dose of 2-4mcg/kg/min was done.

A- The Midodrine treatment group:
Patients were treated by 10mg tds oral midodrine may be increased to 12.5-15mg tds.

B- The octreotide treatment group:
Patients received 50mg subcutaneous octreotide three times daily.

C- The noradrenaline treatment group:
Received a continuous infusion of NA (Levophed; Laboratoire Aguettant, Lyone, France) at an initial dose of 0.5mg/h, designed to achieve an increase in Mean Arterial Pressure (MAP) of at least 10mmHg or an increase in 4-hour urine output to more than 200mL. When one of these goals was not reached, the NA dose was increased every 4 hours in steps of 0.5mg/h, up to the maximum dose of 3mg/h.

Efficacy was assessed on serum creatinine and creatinine clearance, both measured daily. A 30% increase in creatinine clearance or a 30% decrease of serum creatinine were considered a positive response to treatment.

Treatment was administered either until HRS reversal (serum creatinine level below 1.5mg/dl and/or creatinine clearance above 40mL/min), or for a maximum of 5 days.

Study parameters:
The following parameters were recorded before treatment initiation, at baseline (day 0), and on days 1, 3, 5, after treatment initiation: Systolic and diastolic blood pressure, heart rate, CVP, daily urine output, daily urinary sodium excretion, urine creatinine, serum sodium and creatinine (mg/dl) levels, serum bilirubin (mg/dl), INR and the hemoglobin concentration. Adverse events were recorded daily and assessed for their relation to treatment administration.

Statistical analysis: Data were presented as mean and Standard Deviation (SD) values. One way ANOVA test was used to compare between the three groups. Repeated measured ANOVA test was used to study the changes by time within each group. Tukey’s post-hoc test was used for pairwise comparisons between the groups when ANOVA test is significant. Urine output data and percentage of changes in data of all variables showed non-normal (non parametric) distribution so Kruskal-Wallis test was used for comparisons between the groups. This test is the non-parametric alternative to one-way ANOVA test. Mann-Whitney U test was used for pair-wise comparisons between the groups when Kruskal-Wallis test is significant. Friedman’s test was used to study changes by time in Creatinine clearance data because there were only two time periods. The significance level was set at $p<0.05$. Statistical analysis was performed with PASW statistics 18.0® (Predictive Analytics Software) for Windows.

Results
This study included 30 patients (23 males and 7 females) with hepatorenal syndrome who were admitted to the ICU in the following hospitals in the period from 2/2009 to 5/2011:
• Critical Care Medicine Department, Cairo University.
• Tudor Belhars institute.
• Nasser Institute.

The patients age ranged from 52 to 64 years with 5 patients (age 50-55), 17 patients (age 56-60) and 8 patients (age over 60 years). In the Midodrine group the patients age ranged from 54 to 63 years with mean age of 59+1.9 years, while in the Octreotide group age ranged from 52 to 63 years with mean age 58.2+2.2 years and in the Noradrenaline group patients age ranged from 53 to 64 years with mean age 58.4+3.2 years.
The patients had child C liver cirrhosis viral etiology (chronic active hepatitis C infection) with Child score ranging from 10 to 12 and the following parameters.

There was no significant difference between the mean initial body weight in the 3 groups:
- Midodrine group: 70.3±10.2Kg.
- Octreotide group: 70.7±9.3Kg.
- Noradrenaline group: 69.95±11.1Kg.

At the end of treatment period there was significant reduction in body weight in the three groups as observed by the mean body weight in each group at the end of treatment period:
- Midodrine group: 66.15±11.5Kg.
- Octreotide group: 67.95±11.1Kg.
- Noradrenaline group: 60.65±8.86Kg.

Noradrenaline group showed the highest weight reduction among the 3 groups. Although the difference in weight reduction between the difference between the Noradrenaline group and the 2 other groups is statistically significant in the favor of Noradrenaline (p>0.05).

There was no statistically significant difference between mean BP values at baseline in the three groups. There was statistically significant increase in mean BP in the three groups at the end of treatment period.

There was no statistically significant difference in the post treatment values of mean BP between the three although the Noradrenaline group showed the highest rise in mean BP.

The initial mean heart rate was comparable in the three groups with no statistically significant difference. There is no statistically significant difference between the mean heart rate values at the end of treatment in the three groups.

The initial serum sodium (Na) level was comparable in the three groups with no statistically significant difference. At the end of treatment period, there was no statistically significant increase in serum Na level in the midodrine group. In the octreotide group, there was statistically significant increase in serum Na Level (from 121.3±3.5 to 129.4±4.5mEq/L). In the Noradrenaline group, treatment was able to induce statistically significant rise in serum Na level (from 121.6±7.2 to 131.4±5.9mEq/L).

As regard the serum creatinine level, the mean baseline serum creatinine level in the midodrine, octreotide and Noradrenaline groups was 2.8±0.9 mg/dl 2.2±0.5mg/dl and 2.8±0.5mg/dl respectively with no statistically significant difference. In the midodrine group there was no statistically significant change in serum creatinine level from 2.8 ± 0.9 to 2.6±1.2mg/dl. In the octreotide group, there was rise in the mean serum creatinine level at the end of treatment (from 2.2±0.5 to 2.5±1.4mg/dl but the change was not significant statistically. In the Noradrenaline group, there was statistically significant reduction in the mean serum creatinine level at the end of treatment (from 2.8±0.5 to 1.7±0.5mg/dl).

The baseline mean daily urine output (before the start of treatment) was comparable in the three groups with no statistically significant difference. There was statistically significant rise in urine output that was observed in the three groups during the treatment period.

The difference in daily urine output at the end of treatment between the three groups remains insignificant statistically.

The baseline mean creatinine clearance was comparable in the three groups with no statistically significant difference.

Only the Noradrenaline group that showed a statistically significant increase in creatinine clearance at the end of treatment period. The mean creatinine increased from a baseline of 35.2±7.7 ml/min to 59.2±13.8ml/min in the last day of treatment.

In the Noradrenaline group, reversal of hepatorenal syndrome was reached in 6 patients out of 10 (60%) with achieved serum creatinine of 1.5 mg/dl or less. The goal was achieved after 3 days of treatment in ICU in only 2 patients, the other 4 needed to continue treatment till day 5.

In the midodrine group, hepatorenal syndrome was reversed in only 2 patients out of 10 (20%) after 5 days of treatment. Two patients died within the period of treatment (mortality 20%) from: Complications following severe hematemesis and complications of pneumonia in the 3rd & 4th day respectively.

In the octreotide group, only 3 patients out of 10 showed reversal of hepatorenal syndrome (30%) after 5 days of treatment. Mortality was 20%.
Table (2): Mean, Standard Deviation (SD) values and results of comparison between mean BP through different periods within each group.

<table>
<thead>
<tr>
<th>Period</th>
<th>Midodrine Mean ± SD</th>
<th>Octreotide Mean ± SD</th>
<th>Noradrenaline Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>68.5±7.2</td>
<td>72.8±8.1</td>
<td>68.1±5.8</td>
<td></td>
</tr>
<tr>
<td>3rd day</td>
<td>77.3±5.3</td>
<td>76.7±24.9</td>
<td>80.3±24.4</td>
<td></td>
</tr>
<tr>
<td>5th day</td>
<td>78.1±5</td>
<td>80.3±26.2</td>
<td>83.8±5.9</td>
<td></td>
</tr>
</tbody>
</table>

*: Significant at p<0.05, means with different letters are statistically significantly different.

Table (3): Mean, Standard Deviation (SD) values and results of comparison between creatinine level in the three groups.

<table>
<thead>
<tr>
<th>Period</th>
<th>Midodrine Mean ± SD</th>
<th>Octreotide Mean ± SD</th>
<th>Noradrenaline Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>2.8±0.9</td>
<td>2.2±0.5</td>
<td>2.8±0.5</td>
<td>0.160</td>
</tr>
<tr>
<td>3rd day</td>
<td>2.7±1</td>
<td>2.4±0.9</td>
<td>2.3±0.5</td>
<td>0.613</td>
</tr>
<tr>
<td>5th day</td>
<td>2.6±1.2</td>
<td>2.5±1.4</td>
<td>1.7±0.5</td>
<td>0.266</td>
</tr>
</tbody>
</table>

*: Significant at p<0.05.

Table (4): Mean, Standard Deviation (SD) values and results of comparison between urine output in the three groups.

<table>
<thead>
<tr>
<th>Period</th>
<th>Midodrine Mean ± SD</th>
<th>Octreotide Mean ± SD</th>
<th>Noradrenaline Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>228.8±76.8</td>
<td>303.8±90.1</td>
<td>243.8±56.3</td>
<td>0.174</td>
</tr>
<tr>
<td>1st day</td>
<td>697.5±485.8</td>
<td>693.8±466.3</td>
<td>531.3±317</td>
<td>0.660</td>
</tr>
<tr>
<td>5th day</td>
<td>1268±913.8</td>
<td>1112±476.4</td>
<td>1363±377</td>
<td>0.277</td>
</tr>
</tbody>
</table>

*: Significant at p<0.05.

Table (5): Mean, standard deviation (SD) values and results of comparison between creatinine clearance through different periods within each group.

<table>
<thead>
<tr>
<th>Period</th>
<th>Midodrine Mean ± SD</th>
<th>Octreotide Mean ± SD</th>
<th>Noradrenaline Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>36.7±9.7</td>
<td>45.9±11.2</td>
<td>35.2±7.7</td>
<td></td>
</tr>
<tr>
<td>5th day</td>
<td>45.2±21</td>
<td>48.8±21.9</td>
<td>59.2±13.8</td>
<td></td>
</tr>
</tbody>
</table>

*: Significant at p<0.05.

Discussion

Development of HRS is the ultimate consequence of peripheral (mainly splanchnic) arterial vasodilatation, and the constriction of the renal vascular bed is responsible for the manifestations of HRS [8].

Although Jean-Marie Peron et al., in 1999 in their study, concluded that HRS as defined by the International Ascites Club can be treated by albumin administration alone or with furosemide given according to the patient's specific need using CVP, comprehension of the pathophysiology of HRS encouraged the use of vasoconstrictors in the treatment of HRS.
Vasopressor agents have been proposed for the treatment of this condition in conjunction with albumin infusion to correct vascular underfilling. Vasopressin agonists induce vasoconstriction of the splanchnic vascular bed leading to an increase in renal perfusion and glomerular filtration rate. Among the different vasopressin analogues, Terlipressin was the most effective and safe with the least side effects giving the best outcome and the highest incidence of reversal of HRS.

The effects of octreotide were evaluated previously in 2 uncontrolled studies. In the first study by Kaffy F. et al., [10] in 1999, octreotide infused at the rate of 25mcg/h during 5 days resulted in a gradual decrease of serum creatinine, increase in creatinine clearance, and urine output in 4 of 5 cirrhotic patients with HRS. Four patients died within weeks after the end of treatment as HRS recurred rapidly when the octreotide infusion was stopped. In the second study conducted by Angeli P. et al., in 1999 [11], this time not as single vasopressor agent but combined with Midodrine, also not randomized, a group of 5 patients with HRS type 1 was treated with octreotide administered subcutaneously (100 to 200mg, 3 times daily) and the alpha-agonist agent midodrine (7.5 to 12.5mg, 3 times daily) for a period of 20 days; in addition, all these patients received albumin infusions if the central venous pressure was below 12mmHg. Eight patients treated with albumin and nonpressor doses of dopamine administered intravenously were used as a control group. In all patients treated with midodrine and octreotide, an improvement in renal function parameters with concomitant decrease in plasma renin activity, plasma vasopressin, and plasma glucagon was observed within several days. Studies conducted later, Pomier-Layarargues [12] and Kiser [13], showed failure of Octreotide as single vasopressor in treatment of HRS.

Noradrenaline, an adrenergic agonist with powerful vasoconstrictor effect, in several studies, has been shown to be as effective as Terlipressin in the treatment of HRS giving almost same result in improvement of parameters and reversal of HRS (Duvoux C. et al. [14], Alessandria C. et al. [15], and Sharma P. et al. [16]).

Midodrine, an alpha-adrenergic agonist, has also been tested in patients with HRS (Angeli P., et al., [11,17]). Acute oral monotherapy with 15mg of midodrine only slightly improved systemic hemodynamics and failed to improve renal function in patients with type 2 HRS. However, when given in combination with octreotide (an inhibitor of endogenous vasodilators release) and albumin, midodrine administration was associated with a significant improvement in renal function in 5 patients with type I HRS.

In this study, three vasoconstrictor agents were used: Midodrine an oral alpha adrenergic agonist, octreotide a somatostatin analogue that antagonizes splanchnic vasodilatation and Noradrenaline. These agents were combined with albumin and dopamine in nephrogenic dose to combat renal vasoconstriction. Although Midodrine as single agents did not show significant effectiveness in HRS in previous studies, we hoped that midodrine, the cheapest among other agents could be effective as part of triple therapy. The simplicity of octreotide administration and the possibility of positive effect if part of triple therapy has encouraged the reevaluation of Octreotide in treatment of HRS in this study.

Noradrenaline in addition to albumin and nonpressor dose of dopamine was able to induce improvement in all hemodynamic parameters: Mean blood pressure was raised from 68.1±5.8mmHg to 83.8±4.9mmHg, heart rate was reduced from 92±5.4 to 84.5±2.1 bpm, serum sodium level was raised from 121.6±7.9 to 131.4±5.2mEq/L, serum creatinine was lowered from a mean of 2.8±0.5mg/dl with improvement of creatinine clearance from 35.2±7.7 to 59.2±13.8, urine output was increased from a mean of 243.8±56.3 to a mean of 1363.8±377.5ml/day. Noradrenaline in conjunction with albumin and dopamine was able to induce reversal of HRS (defined as serum creatinine of 1.5mg/dl or less) in 6 patients out of 10 (60%) which is comparable to the result obtained with Alessandria [18] (70%) and Sharma’ [16] (50%) who compared Noradrenaline to Terlipressin combined with albumin that succeeded to reverse HRS in 83% and 50% of the patients in the two studies respectively. Our results agrees with the results of the two previous studies that Noradrenaline is as effective as Terlipressin in treatment of HRS. In our study reversal of HRS was achieved in the 3rd day in 2 patients, while the same result was obtained in the 5th day in the remaining 4 patients. In the remaining 4 patients, Noradrenaline improved the serum creatinine level, raised the mean blood pressure, increased urine output, serum sodium level and calculated creatinine clearance with no significant changes in the parameters concerning liver functions (s.bilirubin/INR/child score).

In the Midodrine group, there was statistically significant: Increase in mean blood pressure (68.5±7.2 to 78.1±5mmHg), decrease in heart rate (89.4±6.7 bpm to 83.7±6.6bpm) and induction of diuresis...
(228.8±76.8ml to 1268±913.8ml). The other parameters (serum sodium, serum creatinine and creatinine clearance) showed no statistically significant improvement. This agrees with the study performed by Angeli et al., [17] as midodrine administration resulted in improvement in systemic hemodynamics and urine output in cirrhotic patients either uremic or not, although in uremic patients improvement was to a lesser extent. Renal hemodynamics showed no significant improvement in uremic patients (patients with HRS). As regard final outcome, only 2 patients achieved serum creatinine level of 1.5mg/dl or less in the fifth day of treatment (20%). Mortality during, treatment period was 20% in this group. There was significant increase in blood pressure and urine output, while no statistically significant improvement in the serum creatinine level, serum sodium level and creatinine clearance. There was no significant change in the parameters of liver function (INR/serum bilirubin/child score). In the Octreotide group, the treatment was able to induce significant improvement in: Mean blood pressure (from 72.8 ±8.1 to 80.5±6.1mmHg), heart rate (87.6±3.1 to 83.5±3.9bpm), serum sodium level (121.3±4.5 to 129.4±3.5mEq/L) and urine output (303.8±9.1 to 1112.5±476.4ml/day). There was no significant improvement in serum creatinine level or creatinine clearance. As regard out come, only 3 patients had their serum creatinine level normalized at the end of treatment period. Mortality was 20% during the period of treatment. This result is almost compatible with Pomier-Layarargues [12] and Kiser [13] in the fact that Octreotide as single vasoconstrictor is not effective (alone or combined with albumin) in reversing HRS, although in these studies it showed decrease in 30 day mortality. The parameters of liver function remained with no statistically significant change.

As all patients included in this study were classified as Child C according to the Child-Turcotte-Pugh classification with score ranging from 10-12 and almost no changes occurred throughout the period of treatment, the difference in response in the three groups could not be attributed to any difference in the liver condition between the patients in the three groups. The Noradrenaline group showed the best result as regard the short term outcome mainly reversal of HRS. Mortality cannot be attributed to failure of treatment.

As regard the age, as predictor of favourable response to treatment, the age of those who had reversal of HRS ranged from 53 to 60 with mean age of 55.9±1.9 years which is much lower than the mean age in the 3 treatment groups. From 5 patients with age ranging between 50-55, 4pts had reversal of HRS irrespective of treatment. In the age group 56-60 (17pts) only 7 patients showed reversal of HRS irrespective of treatment. No reversal of HRS observed in patients with age above 60 years (8 patients). Mean serum bilirubin level at the start of treatment was comparable in the 3 treatment groups with no statistically significant difference (2.59mg/dl, 2.46mg/dl, and 2.33 mg/dl). In patients who showed reversal of HRS the mean serum bilirubin level at the start of treatment was 2.28±0.38 which is of no statistically significant difference than the treatment groups.

Conclusion:

The use of Noradrenaline combined with albumin remains an effective treatment for HRS. Noradrenaline is the best alternative for Terlipressin as splanchnic vasoconstrictor with almost similar efficacy and safety profile but better as regard the financial cost. The addition of dopamine infusion to Midodrine or octreotide combined with albumin infusion did not result in significant increase in their efficacy, remaining inferior to Noradrenaline.

Age remains the main predictor of good prognosis in treatment of HRS. Patients at younger age show better response to treatment with greater chance of reversal of HRS.

In this study serum bilirubin level at the start of treatment was not a predictor of good response to treatment in contrast to the conclusion of Nazar et al., [18].

Recommendation:

In future studies it may be worth to try combination of both Midodrine and octreotide (octreotide was proved to potentiate the vasoconstrictor effect of midodrine on splanchnic vessels) in addition to albumin infusion (proved effective in many studies) in comparison to Noradrenaline with albumin. Other agents can be added, such as penotxyfillin (inhibitor of TNF) that showed efficacy in preventing development of HRS in patients with alcoholic cirrhosis.

Both octreotide and midodrine have been tried alone or in combination in HRS with some beneficial effects. Oral midodrine, an alpha-adrenergic receptor agonist, causes vascular smooth muscle vasoconstriction, and subcutaneous octreotide, a long-acting somatostatin analogue, which is used to reduce portal hypertension after variceal hemorrhage. Early studies in Type 2 HRS demonstrated no improvement in renal function with midodrine, [15,11,12]. However, the combination of thrice daily
midodrine 7.5–12.5mg and octreotide 100–200 µg, and albumin, improved renal plasma flow, GFR and urinary sodium excretion with reduction in plasma renin activity, vasopressin and glucagon levels in type 1 HRS after 3 weeks of treatment. Survival was higher compared to type 1 HRS patients treated with albumin and dopamine [12]. Additional studies reported improvement in renal function in HRS using the combination of octreotide and midodrine [19]. A longer acting version of octreotide (given monthly) has also been studied [20], as has the use of transjugular portosystemic shunting after the control of Type 1 HRS using octreotide and midodrine combination [21], with some encouraging results.

References

المملوكة العربية

مكتشفة الكلى الكبيرة في المضاعفات الحادة للتهاب الكبد والتي قد يؤدي إلى نسب عالية من الوفيات دون علاج. وكان هدف هذه
الدراسة هو المقارنة بين فعالية عقار الالوكسيبرتين مقابل عقار الميدروبين أو عقار الالترانتين في علاج الممتلئة.
وقد تم اختيار 150 مريض وتم تقسيمهم إلى ثلاث مجموعات:

المجموعة الأولى تلقى من 10 إلى 15ملغ من عقار الالترانتين عن طريق الفم.
المجموعة الثانية تلقى 15 ملغ من عقار الالترانتين تحت الجلد.
المجموعة الثالثة تلقى عقار الالترانتين في صورة محلول وريدي مستمر بجرعة اولية 5ملغ في الساعة، التي تحقق زيادة في الضغط
الشرعي المتوسط للمريض بمقدار 10ملم، زيادة في كمية البول في 4 ساعات إلى أكثر من 1000مل. عندما لم يتم الوصول إلى أحد
هذه الأهداف يتم زيادة الجرعة بمعدل 5ملغ في الساعة كل 4 ساعات حتى الوصول إلى أقصى جرعة 30ملغ في الساعة.

أظهرت مجموعة الالترانتيني فقط زيادة ذات دلالة إحصائية في تصفية الكرياتينين في نهاية فترة العلاج حيث زادت تصفية الكرياتينين
من خط الأساس 18.6±5.7مل/دقيقة إلى 18.6±5.7مل/دقيقة في اليوم الأخير من العلاج.

في مجموعة الالترانتيني تم الوصول إلى عكس متلازمة الكبد في 6 مرضى من أصل 10 (60%) مع تحقيق الكرياتينين في مصل
الدم من 5 مفيoler أو أقل. وقد حقق هذا الهدف بعد 3 أيام من العلاج في وحدة العناية المركزة في 3 فقط من المرضى، أما ارتفاع
مرضى الأخرين استمر معになولة العلاج حتى اليوم الخامس، وفي مجموعة الالترانتيني، انخفضت متلازمة الكبد في 2 من المرضى
من أصل 10 (20%) بعد 5 أيام من العلاج. في المجموعة الالترانتيني، أظهرت 3 مرضى فقط من أصل 10 عكس متلازمة الكبد (30)
أيام من العلاج.

وستخلصون من ذلك أن الالترانتيني مع الالترانتيني يعتبر علاج فعال ويمكن اعتباره كisdiction من حيث الكفاءة لعلاج الالترانتيني
ومساوئه له الناتجة والأمان. وستخلصون أيضا أن إضافة عقار الالوكسيبرتين أو الالترانتين إلى عقاري الالترانتيني والدوباميني لا يؤدي إلى
زيادة كبيرة في فعاليته.