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Original Research Article

A Comparative Assessment of Norepinephrine and Terlipressin in the Management of Hepatorenal Syndrome

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Abstract

Aim: Assessment of norepinephrine and terlipressin in the management of Hepatorenal Syndrome.

Materials and methods: A total of 40 patients with HRS type 1, presenting at the Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India, were prospectively evaluated. Patients were randomized to either terlipressin or noradrenaline group i.e. half for terlipressin (group A) and half for noradrenaline (group B). Patients in either group received treatment with terlipressin or noradrenaline with 20 g albumin/day. Patients in group A received terlipressin as an intravenous bolus of 0.5 mg every 6 h. Patients in group B received a continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase in MAP of at least 10 mmHg or an increase in 4-h urine output of more than 200 ml. All patients were admitted for 15 days in hospital and followed-up to 30 days. Clinical and biochemical parameters were assessed at baseline, and day 15. An arterial blood sample was collected after overnight fast and bed rest for at least 8 h in supine position for plasma renin activity and aldosterone concentration.

Results: 8 (40%) patients in group A and 10 (50%) in group B responded to therapy. 22 (group A-12; group B-10) patients did not respond to treatment. There was a significant decrease in serum creatinine from baseline in both groups. Mean arterial pressure and urine output increased significantly in both groups at day 15. Plasma renin activity and aldosterone concentrations decreased significantly in both groups at day 15.

Conclusion: In conclusion, norepinephrine and terlipressin had similar response rates or equally effective in cases of hepatorenal syndrome. But this study was based on a small population size. More studies are needed on a large scale to establish this as an alternate drug.

Keywords: Telipressin, noradrenaline, aldosterone, albumin, vasoconstrictors.

Introduction

HRS is now recognized as a form of renal failure that occurs as the consequence of the interplay between various hemodynamic changes in patients with advanced cirrhosis. [1] Hepatorenal syndrome (HRS) is a fatal complication of advanced cirrhosis with ascites and liver failure, with nearly 50% of patients dying within 2 weeks after the onset. [2] Studies have suggested that HRS is functional abnormality in the kidneys and is a potentially reversible syndrome. [1] Therapy with systemic vasoconstrictors and albumin is an effective option to ameliorate renal dysfunction and to improve survival. [3] Terlipressin is the most widely used vasoconstrictor in the world. However, terlipressin is not readily available in several countries and therapy is expensive. By contrast, noradrenaline, a catecholamine with predominantly alpha-adrenergic activity, is widely available and relatively inexpensive.

HRS is sub-classified into types 1 and 2. Type 1 HRS is characterized by rapid progressive renal failure, usually accompanied by multi organ failure. Type 2 HRS manifests itself as a slowly progressive functional renal failure associated with refractory ascites [4]. A 40% premature mortality rate has been reported in type 1 HRS [5] but may be as high as 83% [6]. Mortality associated with type 2 HRS ranges from 20% to 60% [5, 6]. Since the arterial vasodilation seems to be a key mechanism in the pathogenesis of HRS, vasoconstrictors have been used as a bridging therapy leading up to the definitive treatment, liver transplantation. The vasopressin analog terlipressin is the most widely studied drug, especially in type 1 HRS [7]. However, it is expensive and unavailable in many countries. Norepinephrine, a catecholamine with predominantly alpha-adrenergic activity, is widely available, inexpensive and has been used for the treatment of HRS type 1 since 2002 [8].

Methodology:

A total of 40 patients with HRS type 1, presenting at the Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. were prospectively evaluated. Diagnosis of HRS type 1 was based on the criteria of Salerno *et al.* [9].

Inclusion criteria: Patients were cirrhosis with ascites with serum creatinine levels P2.5 mg/dl; absence of shock, fluid losses and treatment with nephrotoxic drug; no ultrasound evidence of renal parenchymal disease or obstructive uropathy and absence of proteinuria more than 500 mg/24 h.

Exclusion criteria: Patients with history of coronary artery disease, ventricular arrhythmia or obstructive arterial disease of limbs were excluded.

Patients were randomized to either terlipressin or noradrenaline group i.e., half for terlipressin (group A) and half for noradrenaline (group B). Patients in either group received treatment with terlipressin or noradrenaline with 20 g albumin/day. Patients in group A received terlipressin as an intravenous bolus of 0.5 mg every 6 h. If a significant reduction in serum creatinine level (P1 mg/dl) was not observed during a 3-day period, the dose of terlipressin was increased in a stepwise fashion every 3 days to a maximum of 2 mg every 6 h. Patients in group B received a continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase in MAP of at least 10 mmHg or an increase in 4-h urine output of more than 200 ml. When one of these goals was not achieved, the noradrenaline dose was increased every 4 h in steps of 0.5 mg/h, up to the maximum dose of 3 mg/h. Albumin was withheld if central venous pressure (CVP) was more than 18 cm of saline. All patients were admitted for 15 days in hospital and followed-up to 30 days. Clinical and biochemical parameters were assessed at baseline, and day 15. An arterial blood sample was collected after overnight fast

and bed rest for at least 8 h in supine position for plasma renin activity and aldosterone concentration. Blood samples were taken from the radial artery, centrifuged at 2500 rpm for 10 min at 3 °C and stored at 80 °C.

Results

There was a significant decrease in serum creatinine from baseline in both groups. Mean arterial pressure and urine output increased significantly in both groups at day 15. Plasma renin activity and aldosterone concentrations decreased significantly in both groups at day 15. 8 (40%) patients in group A and 10 (50%) in group B responded to therapy. 22 (group A-12; group B-10) patients did not respond to treatment. At the end of 15 days of therapy, 8 (40%) patients in group A and 10 (50%) in group B survived. There was no mortality between 15 and 30 days in responders

Table 1: Basic demographic variables of both the groups

Variables	Terlipressin (n = 20)	Noradrenaline (n = 20)
Age (yr)	49.7±7.8	44.5±10.6
Gender (M: F)	14 (70%):6 (30%)	15 (75%):5 (25%)

Table 2: Baseline clinical, hormonal and biochemical variables of both the groups and their p-value

Variables	Telipressin	Noradrenaline	p-value
MELD score	27.04±4.26	24.23±6.22	0.302
Serum albumin (g/dl)	3.10±0.65	3.02±0.54	0.854
Serum bilirubin (mg/dl)	4.20±2.89	5.01±6.22	0.892
Serum sodium (mEq/L)	128.9±5.0	127.6±5.70	0.422
Blood urea (mg/dl)	93.68±21.6	92.50±20.52	0.798
Serum creatinine (mg/dl)	3.34±0.85	3.05±1.00	0.206
Urinary sodium (mEq/L)	47.27±18.56	46.83±19.88	0.834
Urine output/24 hours (ml)	661.5±236.8	640.4±258.5	0.605
Mean arterial pressure (mmHg)	64.4±12.4	64.8±9.75	0.794
Plasma renin activity (ng/ml/h)	37.54±12.87	36.20±11.34	0.635
Plasma aldosterone concentration (pg/ml)	1654.7 ± 774.5	1784.6±625.46	0.492

Table 3: Change in parameters with therapy in both the groups

Parameter	Telepressin group (n=20)			Noradrenaline group (n=20)		
	Baseline	Day 15	p value	Baseline	Day 15	p value
Serum creatinine (mg/dl)	3.34±0.85	1.71 ± 1.23	0.002	3.05±1.00	1.48±0.76	0.000
Urinary sodium (mEq/L)	47.27±18.56	72.0 ± 23.2	0.009	46.83±19.88	75.6±32.7	0.069
Urine output/day (ml)	661.5±236.8	1076 ± 402.4	0.034	640.4±258.5	1421±584	0.004
Mean arterial pressure (mmHg)	64.4±12.4	72.1 ± 13.2	0.021	64.8±9.75	84.6±6.4	0.036
Plasma renin activity (ng/ml/h)	37.54±12.87	11.34 ± 3.0	0.001	36.20±11.34	9.03±2.76	0.000
Plasma aldosterone (pg/ml)	1654.7 ± 774.5	670.2 ± 298.6	0.012	1784.6±625.46	523±280.0	0.001

Urine output and urinary sodium increased significantly and there was a marked suppression of renin-angiotensin-aldosterone system in responders at day 15. There was no significant increase in urine output and urinary sodium in non-responders at day 15. There was also a marked sup- pression of renin-angiotensin-aldosterone system in non- responders at day 15.

Discussion:

Hepatorenal syndrome (HRS) is a fatal complication of advanced cirrhosis with ascites and liver failure, with nearly 50% of patients dying within 2 weeks after the onset. [2] HRS is now recognized as a form of renal failure that occurs as the consequence of the interplay between various hemodynamic changes in patients with advanced cirrhosis. [1] Although HRS is a functional syndrome, it is still associated with a rapid deterioration of multiple organ function and a poor prognosis, especially for type 1 HRS. [9] Liver transplantation is the best treatment of choice for HRS, but both the short life expectancy of HRS and the worldwide organ shortage limits this therapy method. [10] Many treatment methods can be used for hepatorenal syndrome, such as vasoconstrictors and albumin, trans jugular intrahepatic portosystemic stent-shunt, and extracorporeal albumin dialysis, but vasoconstrictors is the most widely used therapy method because of its therapeutic effect and convenience. [11]

In patients with cirrhosis, functional kidney failure is caused by a severe reduction of the effective circulating volume due to splanchnic arterial dilation and a reduction in the renal blood flow due to marked multifactorial intra-renal vasoconstriction [12]. This particular form of renal dysfunction develops in the later phases of liver failure and is characterized by low arterial pressure, intense activation of the renin-angiotensin and sympathetic nervous systems with an increase in the plasma levels of renin, norepinephrine, water retention due to increased anti-diuretic hormone and lowering glomerular filtration rates [13]. Without treatment, short-term mortality exceeds 50% with a median survival time of only 2 weeks [14]. Therapy with systemic vasoconstrictors and albumin is a bridging option to ameliorate renal dysfunction and to improve survival of patients while waiting for definitive treatment with liver transplantation. The rationale of associating these two therapies is to reduce the discrepancy between circulatory capacitance and intravascular volume, thereby increasing the effective arterial blood volume.

Terlipressin promotes vasoconstriction in both systemic and splanchnic circulation through activation of V1 receptors of the vascular smooth muscle cells and is reported to reduce portal inflow, portal systemic shunting [15]; and to dilate intrahepatic vessels, consequently reducing intrahepatic resistance to portal inflow [16].

The overall results of the use of terlipressin in conjunction with albumin in the treatment of HRS are an improvement in renal function and an increase in the median survival time as demonstrated in clinical trials and confirmed by at least three meta-analyses [17, 18, 19]. Although terlipressin has become the vasoactive drug of choice where available, a Cochrane meta-analysis has pointed out that all randomized controlled studies that addressed the efficacy of terlipressin were underpowered and at high risk of bias [17]. Additionally, the evidence on the use of terlipressin in type 2 HRS is scarce since these patients were included in only one trial [20]. Norepinephrine, an inexpensive a-adrenergic receptor agonist available worldwide, is a possible alternative treatment for HRS because its intense vasoconstriction action may increase the effective arterial blood volume. A pilot single-center study with 12 patients demonstrated the reversal of HRS in 10 (83%) patients [21].

Conclusion:

In conclusion, norepinephrine and terlipressin had similar response rates or equally effective in cases of hepatorenal syndrome. But this study was based on a small population size. More studies are needed on a large scale to establish this as an alternate drug.

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