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Comparative Study of Slow Infusion versus Bolus Doses of Albumin and Furosemide Infusion to Mobilize Refractory Ascites in Decompensated Chronic Liver Disease

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ABSTRACT

Background: Combined use of furosemide with albumin is an approved therapy to overcome diuretic resistance in treatment of ascites in decompensated chronic liver disease. Bolus dosing of diuretics has its own limitations due to pre-existing hypotension, post diuretic sodium retention and braking phenomenon. Slow albumin and furosemide Infusion has been shown to mobilize large ascites with improved diuresis and hemodynamic stability in decompensated chronic liver disease. This study was undertaken to compare efficacy and safety of infusion therapy vs bolus therapy in term the management of refractory ascites.

Methods: Decompensated chronic liver disease patients with refractory ascites were randomly assigned into two groups of 15 each - Bolus therapy (intravenous albumin and furosemide as boluses) and Infusion therapy (furosemide infusion at 2mg/hour and albumin at 2g/hour for three days). Diuresis, natriuresis, change in abdominal girth and body weight, and hemodynamic stability (change in SBP) were compared between the two groups.

Results: Infusion therapy, as compared to bolus therapy, showed a significantly better diuresis (mean urinary output increment 483ml vs 243ml, $p < 0.001$), natriuresis (mean urinary sodium excretion increment 35.2 mEq/L vs 16.6 mEq/L, $p = 0.004$), decrease in abdominal circumference (6.1cm vs 3.0cm, $p < 0.001$) and decrease in body weight (5.53 Kg vs 2.86 Kg, $p < 0.001$). The complications of renal impairment were also lower in the Infusion group.

Conclusion: Infusion of furosemide and albumin is a potential safer and effective therapeutic option in the management of refractory ascites with better natriuresis, higher urine output, and higher decrement in abdominal circumference and body weight, and lesser side effects.

Keywords: Bolus dose; continuous infusion; decompensated chronic liver disease; refractory ascites.

INTRODUCTION

Ascites is the most common presentation of decompensated CLD.[1] Treatment modalities for ascites have their own limitations and complications.[2-5] Combined use of furosemide and albumin has shown better results in different conditions of fluid overload than furosemide alone.[6-8] Bolus dosing is limited by pre-treatment hypotension and complications.[9] Few studies show improved diuresis and hemodynamic stability with slow infusions of albumin and furosemide in refractory ascites.[10,11]

With furosemide boluses, sodium excretion declines progressively after first 1-2 hours with post-diuretic compensatory sodium retention.[12,13] Continuous infusion maintains an effective rate of furosemide metabolism and inhibition of sodium retention over time with 30% increase in sodium excretion.[14] Meta-analysis were of the opinion that infusions were more effective than intermittent boluses.[15]

This study was done to compare the efficacy (ascites fluid mobilization, abdominal girth reduction, diuresis/natriuresis) and safety (hemodynamic stability and dyselectrolytemia) of slow infusions with standard bolus therapy in the management of ascites in decompensated CLD.

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METHODS

This was a quasi-experimental study and was carried out at the Department of Gastroenterology, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal after IRB approval. 30 patients (15 in Infusion Group and 15 in Bolus Therapy Group) admitted to the hospital meeting the criteria during the period from August 2017 to August 2018 were studied. Written informed consent was taken from each patient or their relatives prior to enrollment in study. Patients were selected by non-probability sampling.

Patients of decompensated CLD, aged ≥18 years, who were hemodynamically stable for at least 24h (absence of persistent [>1h] hypotension [systolic blood pressure <90 mmHg), not currently on vasopressors, with hypoproteinemia (serum albumin <30g/L or total protein < 60 g/L) and requiring diuresis for refractory ascites, those not responding to diuretics alone were included in the study.

Patients aged < 18 years, those with pregnancy, Acute kidney injury (increase in serum creatinine > 0.3 mg/dl in 48 hours) without any improvement in past 24 hours, or otherwise expected to necessitate dialysis within 48 hours in opinion of treating physician, Chronic kidney disease, hepatic encephalopathy, active UGI bleed, spontaneous bacterial peritonitis (SBP), pre-treatment sodium <125 mEq/L, any previous hypersensitivity to albumin or furosemide and those who didn't give consent were excluded.

Patients in Infusion Group received furosemide infusion at 2 mg/hour and albumin 2g/hour for 3 days while patients in Bolus Therapy Group received similar cumulative dosage divided in boluses (furosemide 40mg twice a day and albumin 20g BD for 3 days). Patients were assessed for diuresis and hemodynamic stability (systolic BP and urine output at 24 hours). Urine sodium (UNa), Abdominal girth (AG), Body weight (BW), systolic BP and urine output were assessed at 72 hours. We compared urinary sodium (UNa), Abdominal girth and body weight before and after 72 hours of initiating therapy in the two groups for measurement of diuresis.

Statistical analysis was performed using IBM SPSS (Statistical Package for Social Science) software. Descriptive statistics were expressed as mean (range) or number (%). Comparison of pre-treatment and post-treatment variables was done using paired samples t-tests. Ninety-five percent confidence intervals were used in all analyses.

RESULTS

A total of 30 patients admitted in medical wards with the diagnoses of decompensated CLD with refractory ascites were divided into two groups (Bolus Group and Infusion Group) of 15 each. All the baseline characteristics were comparable between the two groups - Bolus and Infusion group as summarized in the following table (Table 1).

Table 1. Table showing comparison of baseline characteristics of the patients included in the two groups - Bolus and Infusion group.

Variables	Bolus group (N=15)	Infusion group (N=15)	P value
Age	53 (74-40)	55 (74-40)	0.7
Sex Male Female	 12 (80) 3 (20)	 13 (87) 2 (13)	
Alcohol consumer	13 (87)	13 (87)	
Hemoglobin (g/dl)	10 (7-13)	10 (7-11)	0.43
Platelet ($\times 10^3$/cu mm)	107 (31-175)	110 (39-153)	0.84
Serum Sodium (mEq/l)	134 (126-143)	131 (125-140)	0.40
Serum potassium (mEq/l)	4.2 (3.7-5.2)	4 (3.5-4.5)	0.50
Blood urea (µmol/l)	5.6 (2.3-9)	4.8 (3-8)	0.18
Creatinine (µmol/l)	74 (30-99)	74 (50-99)	0.94
Total Bilirubin (mmol/l)	77 (21-131)	80 (33-178)	0.83
ALT (U/L)	86 (11-207)	55 (14-127)	0.08
AST (U/L)	142 (21-399)	127 (26-255)	0.68
ALP (U/L)	229 (58-453)	219 (80-460)	
GGT (U/L)	97 (24-294)	105 (19-248)	0.77
Serum albumin (g/l)	24 (19-30)	24 (18-29)	0.73
INR	1.8 (0.9-3.3)	1.7 (1.2-2.6)	0.49
USG abdomen Moderate ascites Severe ascites	 12 (80) 3 (20)	 9 (60) 6 (40)	0.82
MELD score	19 (6-37)	18 (9-23)	0.42
MELD-Na score	21 (6-38)	21 (13-30)	0.90
CTP score B C	 8 (53) 7 (47)	 5 (33) 10 (67)	
Urinary Sodium (UNa) in mEq/L	41 (20-69)	35 (17-66)	0.28
Urinary output in ml	1080 (500-2000)	983 (600-1800)	0.93
Abdominal girth in cm	92 (78-113)	96 (76-117)	0.33
Body weight in kg	61 (45-88)	60 (40-85)	0.88
Systolic Blood Pressure (mm hg)	103 (90-130)	105 (90-130)	0.72

Patients were treated with either boluses of furosemide

and albumin or with infusions of furosemide (2mg/h) and albumin(2g/h) for 72 hours.

Table 2. Table showing comparison of characteristics of the patients at initiation of therapy and 72 hours of therapy in the two groups - Bolus group and Infusion group.

Variables	Bolus Group (N=15)		Infusion Group (N =15)	
	0 hour	72 hours	0 hour	72 hours
Urinary sodium (UNa) in mEq/l	41 (20-69)	50 (24-88)	35 (17-66)	70 (18-145)
Urinary output in ml	1080 (500-2000)	1426 (800-2700)	983 (600-1800)	1450 (1000-2500)
Abdominal girth in cm	92 (78-113)	89 (76-109)	96 (76-117)	90 (73-111)
Body weight in Kg	61 (45-88)	58 (44-85)	60 (40-85)	57 (35-80)
Systolic BP in mmHg	103 (90-130)	100 (80-130)	105 (90-130)	101 (90-134)

The mean urinary sodium excretion increment after 72 hours of therapy in the Infusion group (35.2 mEq/L) was significantly higher (p=0.004) than Bolus group (16.6 mEq/L).

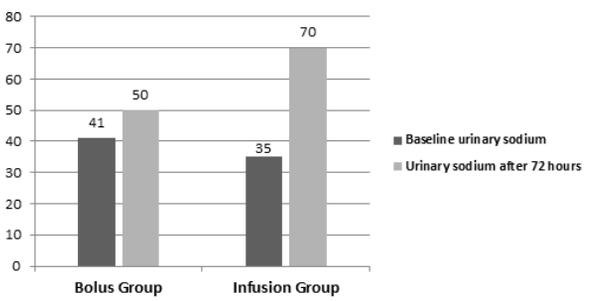

Figure 1. Bar diagram showing comparison of urinary sodium excretion.

The mean increment in urine output at 24 and 72 hours in Bolus group was 140 ml and 250 ml respectively. In Infusion group, mean urine output increment at 24 and 72 hours was 243 and 483 ml respectively. There was significantly higher urine output in Infusion group compared to Bolus group at both 24 and 72 hours of initiation of therapy (p<0.001; p<0.001).

There was significantly higher decrement in abdominal circumference at 72 hours in Infusion group as compared to bolus group (6.1 cm vs. 3.0 cm, p <0.001). Also, significantly more decrement in weight in Infusion group than bolus group after 72 hours of therapy (2.86 kg vs. 5.5 kg, p<0.001) was noted.

The mean of their urine output, abdominal girth, body weight and urinary sodium at initiation of therapy and after 72 hours were compared (Table 3).

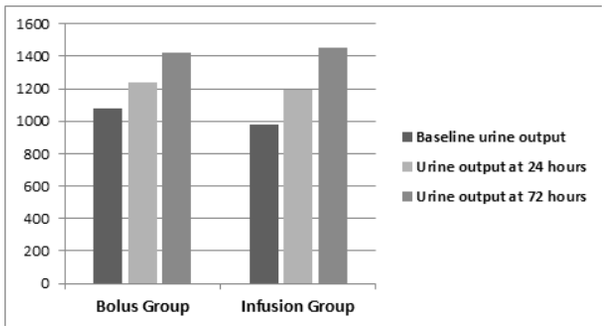

Figure 2. Bar diagram showing comparison of urine output after 24 and 72 hours of therapy.

There was no incidence of hemodynamic instability in both the group during the period of therapy. There were three events of acute kidney injury seen after third day of therapy in bolus group (serum creatinine was seen to increase by > 50% of baseline after 72 hours of therapy).

Table 3.Table showing comparison of mean difference in characteristics values at 72 hours of therapy from baseline in two groups.

Variables	Bolus group (N=15)	Infusion group (N=15)	P value
Increase in Urinary Sodium (UNa) in mEq/l	16.60	35.20	0.004
Increase in Urine output in ml	243	483	<0.001
Decrease in Abdominal girth (AG) in cm	3.0	6.1	<0.001
Decrease in body weight (BW) in kg	2.86	5.53	<0.001

DISCUSSION

In our study, patients receiving infusions of albumin and furosemide over a period of 3 days showed a significantly better diuresis and natriuresis (p = 0.004; p < 0.001) as compared to bolus doses. Infusion therapy also resulted in a significant decrement in abdominal circumference and body weight (p< 0.001; p <0.001) than bolus doses.

Among the several complications of chronic liver disease (CLD), ascites is the most common. Due to altered hemodynamics, splanchnic vasodilation and hyperdynamic state, decompensated CLD patients usually have blood pressure in the lower range. Decompensated CLD is a state of chronic inflammation with increased circulating levels of pro-inflammatory cytokine and chemokine.[16] These pro-inflammatory markers along with certain bacterial products attach with receptors of immune cells that once activated, release pro-inflammatory molecules, along with reactive oxygen and

nitrogen species. This series of events contributes to the development of circulatory dysfunction and, along with it, promotes the development of multi- organ failure.[17]

Due to the associated complications and limiting factors associated with bolus therapy of diuretics, there has been recent advocacy in the literature about the use of infusions of furosemide and albumin. This can overcome the limitations of bolus use of furosemide and albumin, while at the same time improving diuresis and natriuresis.[10,11,15,18] It is more so useful in cases of refractory ascites where, there can be diuretic resistance. The causes of diuretic resistance include poor adherence to drug therapy or dietary sodium restriction, pharmacokinetic issues, and compensatory increases in sodium reabsorption at nephron sites that are not blocked by the diuretic.[19]

Studies with slow infusion of albumin and furosemide infusion over bolus infusion in decompensated chronic liver disease, have initially come up with encouraging results in regards to mobilizing ascites, overcoming diuretic resistance and improving hemodynamic stability.[10,11,18] Major advantages of infusions of albumin and furosemide are postulated as the improved hemodynamic stability, where the drugs can even be used in patients with low BP (SBP<90 mm hg) which is the usual range in patients of decompensated CLD. Post-diuretic sodium retention can also be overcome by continuous infusion.

Few studies comparing albumin and furosemide infusions and terlipressin with standard medical therapy are available. In a study, by Pande et. al (n=41), marked improvement in urine output, urinary sodium excretion and weight loss was observed with continuous infusions of albumin and furosemide.[10] In our study also continuous infusion group showed marked improvement, in terms of urine output, urinary sodium excretion, weight loss and reduction in abdominal girth, without any significant side effect in that group.

In another study by Pande et. al (n=70), although slow infusions of albumin and furosemide was seen to be safe and effective, 51 among the 70 patients needed addition of terlipressin in the regimen.[11] In our study we did not add terlipressin to the regimen. In another study by the same author (n=84), addition of noradrenaline and terlipressin to infusions of albumin and furosemide was found to be non-inferior to terlipressin plus infusions of albumin and furosemide in patients with acute-on-chronic liver failure (ACLF).[19] Another study in patients with ACLF (n=240) showed significantly higher 28 day survival in patients treated with infusions of albumin and furosemide than those treated with standard medical therapy (88.4% vs 66%, p =0.001).[20]

Standard medical therapy for ascites in decompensated CLD is often associated with complications like electrolyte imbalance (hyponatremia, hypokalemia, and hypomagnesaemia), hepatic encephalopathy and renal failure.[21] Three patients in the bolus group in our study also developed acute kidney injury. No such event was seen in the infusion group.

A review article by Elwell et. al states that the combination of furosemide and albumin may remain a safe therapeutic option that provides clinical benefit for the hypo-albuminemic patient with recalcitrant edema or ascites.[6] The results of this study corroborated with the findings from other studies done on albumin and furosemide infusion. However, this study was not blinded. So, for robust analysis, more strict and blinded study with placebo control would have been a better study design. Also, the sample size of our study was small, so studies with larger study population would be required to substantiate our result.

CONCLUSIONS

Our study showed continuous infusion of furosemide and albumin resulted in better natriuresis, higher urine output, increased decrement in abdominal circumference and body weight without development of any side effects proving it to be a potential safer and effective therapeutic option in management of refractory ascites.

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