Effect of 4% Gelofusine Plus Antibiotics on Renal Impairment and Mortality in High-risk Cirrhotic Patients with Spontaneous Bacterial Peritonitis

Siam Sirinthornpunya MD*,
Krongthip Luangvichcharoen MD*

** Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand*

Background: *Spontaneous bacterial peritonitis (SBP) increases the rates of renal impairment and mortality in cirrhotic patients. A previous study showed that cefotaxime plus albumin treatment decreased renal impairment more than antibiotic treatment alone in patients with serum bilirubin > 4 mg/dL or creatinine > 1 mg/dL. 4% Gelofusine is a colloidal volume replacement fluid used for fluid resuscitation and hemodynamic stabilization. Only one study showed that intravenous 4% gelofusine plus antibiotic could decrease the rates of renal impairment and mortality in comparison with the treatment with albumin plus antibiotic in high-risk cirrhotic patients with SBP.*

Objective: *To evaluate the effects of 4% gelofusine plus antibiotics on renal impairment and mortality rates in high-risk cirrhotic patients with spontaneous bacterial peritonitis.*

Material and Method: *Eighteen cirrhotic patients with SBP and serum bilirubin > 4 mg/dL or creatinine > 1 mg/dL were enrolled. Ceftriaxone was given intravenously in doses of 2 g/day. Gelofusine 4% was given intravenously at 1.5 g/kg of body weight at the time of the diagnosis, followed by 1 g/kg on the 3rd day. Renal impairment and mortality rates were evaluated during and after treatment.*

Results: *Five patients (27.8%) had pre-existing renal failure. Infection resolved in 15 patients (83.3%). Renal impairment developed in three patients (16.7%), and six patients (33.3%) died during hospitalization. After one month, the mortality rate was 33.3% (a total of 6 deaths). Patients with renal impairment had higher levels of plasma renin activity than those without renal impairment but the values were not statistically significant.*

Conclusion: *In high-risk cirrhotic patients with spontaneous bacterial peritonitis, treatment with 4% gelofusine intravenously plus antibiotic reduced the incidence of renal impairment but did not reduce mortality in comparison with previous studies. Studies with larger sample sizes may be useful to evaluate these effects.*

Keywords: *Spontaneous bacterial peritonitis (SBP), Renal impairment, 4% gelofusine*

J Med Assoc Thai 2013; 96 (Suppl. 3): S77-S83
Full text. e-Journal: *http://jmat.mat.or.th*

Spontaneous bacterial peritonitis (SBP) occurs in 10-30% of patients with cirrhosis and ascites[1,2]. Even with intensive treatment, the mortality rate varies from 10% to 30%[3]. Cirrhotic patients with SBP had increased ascitic fluid, serum level of cytokines and nitric oxide (NO) synthesis that aggravated splanchnic vasodilation, reduced systemic vascular resistance, activated the renin-angiotensin system and caused renal impairment[4,5]. One-third of patients with SBP developed renal impairment associated with high mortality[3,6]. One study showed that administration of intravenous albumin with cefotaxime reduced the risk of renal failure from 33 to 10% and reduced mortality from 29 to 10%[7]. Another study showed that serum bilirubin > 4 mg/dl or serum creatinine > 1 mg/dl were risk factors of these complications[8]. Because of the risk of infectious disease transmission and the high cost of albumin, further studies have been done to determine whether treatment of SBP with other artificial plasma expanders and antibiotics in patients with SBP would have similar beneficial effects on renal function and survival.

Gelofusine is a colloidal volume replacement fluid based on 4% succinylated gelatin. Gelofusine is iso-oncotic, with theoretical osmolarity of 274 mOsm/L, and the initial volume effect after infusion corresponds to the volume infused[9]. The effect lasts about

Correspondence to:
Sirinthornpunya S, Division of Gastrointestinal, Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, 2 Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: 0-2354-8108 ext. 5101
E-mail: s_sirinthorn@yahoo.com

4 hours[9]. The molecules of gelofusine are stretched during the succinylation process, so that they occupy more space than a non-succinylated gelatin. Gelofusine has been used for fluid resuscitation, hemodynamic stabilization in orthopedic and abdominal surgery, cardiopulmonary bypass, and septic shock. It has a minimal effect on the coagulation system and low hypersensitivity reaction[10]. A prior study showed that intravenous 4% gelofusine plus antibiotics in high-risk cirrhotic patients with SBP decreased the rates of renal impairment and mortality more than treatment with albumin plus antibiotic, but measurements of plasma rennin activity before and after treatment to analyse circulatory dysfunction were not done[11].

The present study aimed to evaluate the rates of renal impairment and mortality in high-risk cirrhotic patients with SBP who were treated with 4% gelofusine and ceftriaxone, and compare plasma renin activity both before and after treatment.

Objective

The present study aimed to assess the effect of 4% gelofusine and antibiotics on renal impairment and mortality rates 7 days and 1 month after treatment in high-risk cirrhotic patients with SBP (serum bilirubin > 4 mg/dL and/or serum creatinine > 1 mg/dL).

Material and Method

Eighteen cirrhotic patients with SBP and serum bilirubin > 4 mg/dL or creatinine > 1 mg/dL admitted to Rajavithi Hospital between December 2010 and January 2012 were enrolled. The protocol for this research was approved by the institutional ethics committee of Rajavithi Hospital, and written informed consent was obtained from the patients. The inclusion criteria were patients who: were aged between 18 and 80 years old; had a diagnosis of cirrhosis based on clinical, biochemical, ultrasonographic and D or histological criteria; had polymorphonuclear cell count in the ascitic fluid > 250 mm^3; and had serum creatinine > 1 mg/dL, and/or serum bilirubin > 4 mg/dL. The patients with any of the following criteria were excluded from the present study: secondary peritonitis, antibiotic treatment within 1 week of the diagnosis of SBP (except for prophylaxis with quinolones); previous abdominal paracentesis within 1 week of the diagnosis of SBP; active GI bleeding within 1 week of enrollment; other infection or septic shock; hepatocellular carcinoma or human immune deficiency infection; advanced hepatic encephalopathy; heart failure; or findings suggestive of organic nephropathy (proteinuria, hematuria, or abnormal findings on renal ultrasonography).

Fifteen patients were excluded for the following reasons: serum bilirubin < 4 and serum creatinine < 1 mg/dL (6 patients), pervious antibiotic treatment (2 patients), septic shock (3 patients), advanced hepatic encephalopathy (2 patients) and hepatocellular carcinoma (1 patient).

Definitions

SBP: cirrhotic patient with ascites fluid analysis showing absolute neutrophil count of more than 250 cell/mm^3 and more than 50% of total white blood cells.

Pre-existing renal failure: patients who had serum creatinine > 1.5 mg/dL or BUN > 30 mg/dL before treatment.

Renal impairment after spontaneous bacterial peritonitis (SBP-RI)

In patients without pre-existing renal failure at enrollment: blood urea nitrogen or serum creatinine level increased by more than 50% of the pre-treatment value to a level higher than 30 mg/dL or 1.5 mg/dL, respectively.

In patients with pre-existing renal failure: increase in the BUN or serum creatinine levels by more than 50% from baseline.

Hyponatremia: serum sodium less than 130 mEq/L.

SBP resolution : all clinical signs of infection had disappeared, polymorphonuclear cell count in ascitic fuid was less than 250 cells/mm^3 and ascitic fuid culture had converted to negative.

Protocol

Baseline data, physical examination, chest x-ray, electrocardiography, complete blood count, liver function tests, renal function tests, urine analysis, and electrolyte tests were performed before treatments. Plasma renin activity (PRA) was measured on the 1st and 7th day of treatment. Laboratory measurements were repeated and then done weekly until discharge. Ascitic fluid samples and blood samples were extracted before treatment for bacterial culture. Patients were treated with intravenous ceftriaxone of 2 grams per day. The ceftriaxone dose was adjusted based on the individual's renal function test. Antibiotic treatment was given for a minimum of 7 days or until resolution of infection. Repeated abdominal paracentesis was performed on the 2nd day if the patient's clinical condition had not improved. If the patient did not respond to treatment,

the antibiotic therapy was modified either empirically or based on the in vitro susceptibility of causative microorganisms. 4% gelofusine at a dose of 1.5 g/kg/day was administered on the first day of admission, followed by another dose of 1 g/kg/day on the 3rd day.

Patient's diuretic and nephrotoxicity drugs were stopped until resolution of infection. Unnecessary abdominal paracentesis was avoided if it was not indicated. Follow-up clinical tests, side effect of treatments and laboratory tests were performed on the 3rd, 7th and 30th day during the treatment.

Patients were excluded from the present study if their serum sodium level increased more than 10 mEq/L from the baseline or heart failure occurred due to volume overload effect.

Statistical analysis

The endpoints of the present study were the incidence of renal impairment and mortality rates during hospitalization and after 1 month. Variables significantly associated with renal impairment and mortality in univariate analysis (using Chi-square test or Fisher's exact test for categorical data and Mann-Whitney U test for continuous data) were analysed by multivariate analysis. Results were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for non-normal distribution datas. Multivariate analysis was performed by multiple logistic regression. The actuarial probability of mortality after 30 days was calculated by the Kaplan-Meier curves. Results were considered statistically significant if the p-value was ≤ 0.05. All analyses were performed using the SPSS statistical package (SPSS Inc., version 17.0, Chicago, IL, USA).

Results

Baseline characteristics

Patients' clinical and laboratory data at the time of SBP diagnosis are shown in Tables 1 and 2. On admission, three patients (16.7%) had hyponatremia. Cirrhotic severity assessed by Child-Turcotte-Pugh score was 11.1 ± 1.4. The infection resolved in most of the patients (83.3%). The ascitic fluid cultures were positive in two patients (11.1%), and hemoculture was positive in six patients (37.9%) as shown in Table 3.

Laboratory data and renal function

At the time of admission, 5 patients (27.8%)

Table 1. Baseline characteristics (n = 18)

Characteristics	Number	Percent
Age (years)		
Mean ± SD	50.78 ± 6.82	
Gender		
Female	6	33.3
Male	12	66.7
Child-turcotte-pugh score		
Mean ± SD	11.11 ± 1.41	
Child A	0	0.0
Child B	2	11.1
Child C	16	88.9
Cause of cirrhosis		
Alcohol	10	55.6
Alcohol and HBV	3	16.7
Alcohol, HBV and HCV	1	5.6
HBV	1	5.6
HCV	1	5.6
PBC	1	5.6
Cryptogenic	1	5.6
Heart rate (beat/min)		
Mean ± SD	100.83 ± 12.44	
Mean arterial pressure (mmHg)		
Mean ± SD	81.44 ± 10.42	

HBV = Hepatitis B virus, HCV = Hepatitis C virus, PBC = Primary biliary cirrhosis

Table 2. Baseline laboratory data

Laboratory	Mean ± SD
Hematocrit (%)	29.60 ± 5
White Blood cell (mm^3)	10,522.20 ± 5,865.8
Platelets (mm^3)	105,150.00 ± 68,176.1
Prothrombin time (min)	18.70 ± 5.4
International ratio (INR)	1.60 ± 0.5
Total bilirubin (mg/dL)	7.20 ± 7.4
AST (UI/L)	83.10 ± 60.9
ALT (UI/L)	36.60 ± 17.2
Alkaline phosphatase (UI/L)	149.70 ± 96.2
Serum albumin (g/dL)	2.20 ± 0.4
BUN (mg/dL)	23.40 ± 14.9
Serum creatinine (mg/dL)	1.10 ± 0.5
Serum sodium (mEq/L)	134.30 ± 5.6
Hyponatremia (n,%)	3/18 (16.7%)
Serum potassium (mEq/L)	3.70 ± 0.6

Table 3. Bacteriologic data

Hemoculture	Number	Percent
Hemoculture		
Negative	12	66.7
Positive	6	33.3
Aeromonas	1	5.6
E. coli	1	5.6
E. coli (ESBL)	1	5.6
E. coli and *vibrio*	1	5.6
Klebsiella pneumoniae	1	5.6
S. bovis	1	5.6
ascites culture		
Negative	16	88.9
Positive	2	11.1
E. coli	1	5.6
E. coli (ESBL)	1	5.6

had pre-existing renal failure. On the 7th day, the patients' mean serum creatinine, blood urea nitrogen (BUN), serum sodium and PRA had not changed since admission, and only mean arterial pressure had increased significantly (p = 0.027) as shown in Table 4. After treatment, three patients (16.7%) developed renal impairment on the 7th day. None of them had pre-existing renal failure on admission. Univariate analysis showed that baseline creatinine (p = 0.049), baseline hematocrit (p = 0.033) and serum AST (p = 0.038) were predictive factors of renal impairment. But in the multivariate analysis, none of these predictive factors were statistically significant.

PRA level

PRA level of the patients with SBP-RI was higher than the group without SBP-RI, but there was no statistical significance (p = 0.109) as shown in Table 5.

Renal improvement

Three of the five patients with renal failure at admission had it resolved by treatment with antibiotic plus plasma expansion. The other two patients with renal impairment died of infection.

Mortality

Six patients (33.3%) died during hospitalization. The causes of death were sepsis (n = 3), pneumonia (n = 2) and recurrent SBP (n = 1). Univariate analysis showed that only serum AST (p = 0.015) and serum ALT (p = 0.024) were predictors of mortality. But in the multivariate analysis, none of these risk factors was statistically significant. The cumulative probability of survival shown in the Kaplan-Meier curve after 30 days was 66.7% (Fig. 1). The major causes of death were sepsis and pneumonia. All patients with SBP-RI died (100.0%), but in patients without SBP-RI, the mortality rate was lower (20.0%) as shown in Table 6.

Discussion

Renal impairment associated with spontaneous bacterial peritonitis is probably caused by hemodynamic change associated with arteriolar vasodilation from release of nitric oxide[4,5]. As a result, a severe reduction in effective arterial blood volume develops, leading to activation of the renin-angiotensin and sympathetic nervous systems[6]. These processes produce vasoconstriction in essential organs, especially the kidneys, leading to renal hypoperfusion and renal impairment.

A previous study by Sort et al about the effect of albumin plus antibiotic treatment in SBP found that intravenous albumin administration prevented haemodynamic deterioration and reduced the rate of renal impairment from 33.0% to 10.0%, and the mortality rate from 29.0% to 10.0%[7]. A recent study of SBP of patients with serum bilirubin < 4 mg/dL and serum creatinine < 1 mg/dL on admission found that they had a low risk of renal impairment and mortality when they received antibiotic treatment without intravenous albumin infusion[8]. The use of plasma expanders with antibiotics in high-risk SBP patients has now become standard treatment[10].

The author found that the incidence of renal

Table 4. Comparison of laboratory data between 1st day and 7th day

Laboratory	Day 1st	Day 7th	p-value
MAP (mmHg)	81.40 ± 10.4	86.90 ± 7.2	0.030*
BUN (mg/dL)	23.40 ± 14.9	25.30 ± 22.8	0.960
Cr (mg/dL)	1.10 ± 0.5	1.20 ± 0.8	0.410
Serum sodium (mEq/L)	134.40 ± 5.7	136.20 ± 8.9	0.290

* = Significant at $p < 0.050$. Values are represented as Mean ± SD

Table 5. Comparison of PRA between day 1st and day 7th

Characters	Day 1st	Day 7th	p-value
Patients with SBP-RI (ngmL/h)	24.2 (8.8-27.2)	40.3 (21.6-90.0)	0.109
Patients without SBP-RI (ngmL/h)	17.4 (2.97-22.4)	5.8 (2.3-22.0)	0.865
Total (ngmL/h)	8.3 (3.5-23.0)	13 (3.3-30.5)	0.472

Values are represented as median with interquartile range (IQR) for non-normal distribution

Table 6. Mortality in patients with or without SBP-RI

Characters of the patients	Number	Mortality rate (%)
Patients with SBP-RI	3	100.0
Patients without SBP-RI	15	20.0
Total	18	33.3

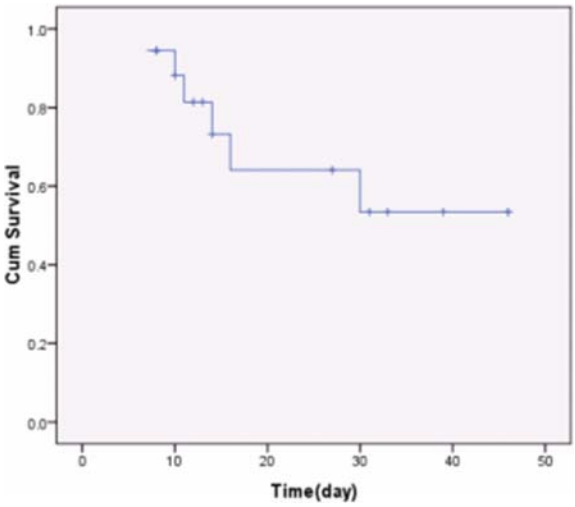

Fig. 1 Cumulative probability of survival shown in the Kaplan-Meier curve at 30 days

impairment in the present study was comparable with that of a previous study which used the same treatment (16.7% vs. 13.8%)[11], but it was higher than in another study which used albumin plus antibiotic (16.7% vs. 10%)[7]. There was improvement in MAP after treatment that indicated circulatory improvement, but there was no change in PRA. This finding indicated that gelofusin has some effect on haemodynamic improvement but its effect is not as strong as that of albumin. The same finding was also seen in the study of the administration of albumin vs. hydroxyethyl starch in patients with SBP[12]. The study found that albumin increased arterial pressure and brought about greater suppression of PRA, but no significant changes were observed in patients who were treated with hydroxyethyl starch[12].

In the present study, the in-hospital mortality and the 1-month mortality rate were equally 33.3% which are higher than in the previous studies by Sort, et al[7] and by M. Cartier et al[11]. The different results may be due to differences in study design and patient characteristics. The patients with SBP-RI had a higher mortality rate than the group of patients without SBP-RI. With regard to gelofusine administration, the sodium and volume infused were higher than with albumin. Careful monitoring of the volume expansion in cirrhotic patients is recommended. Fortunately, no severe adverse effects from gelofusine administration

were found in the present study.

The cost of treatment with albumin is 7 times higher than the cost of 4% gelofusine. The use of 4% gelofusine instead of albumin in high-risk SBP patients may be a reasonable alternative.

Conclusion

In high-risk cirrhotic patients with spontaneous bacterial peritonitis, treatment with 4% gelofusine intravenously plus antibiotic reduces the incidence of renal impairment but does not reduce mortality in comparison with previous studies. Studies of larger sample sizes may be useful to evaluate these effects.

Potential conflicts of interest

None.

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ผลของการให้ 4% gelofusine ร่วมกับยาปฏิชีวนะต่อการทำงานของไตและอัตราการเสียชีวิตในผู้ป่วยตับแข็งที่มีการติดเชื้อในช่องท้องแบบปฐมภูมิในกลุ่มที่มีความเสี่ยงสูง

สยาม ศิรินธรปัญญา, กรองทิพย์ เหลืองวิชชเจริญ

***ภูมิหลัง**: การติดเชื้อในช่องท้องแบบปฐมภูมิเพิ่มอัตราการเกิดไตวายและเพิ่มอัตราการเสียชีวิตในผู้ป่วยตับแข็ง การศึกษาก่อนหน้านี้พบว่าการให้ยาปฏิชีวนะ ceftriaxone ร่วมกับการให้อัลบูมินสามารถลดการเกิดไตวายและลดอัตราตายในผู้ป่วยตับแข็งที่มีระดับบิลิรูบินมากกว่า 4 มิลลิกรัมต่อเดซิลิตร หรือระดับครีเอตินีนในเลือดมากกว่า 1 มิลลิกรัมต่อเดซิลิตร 4% gelofusine เป็นสารกลุ่มคอลลอยด์ที่ใช้เป็นสารน้ำทดแทนและรักษาภาวะสมดุลของร่างกาย การศึกษาหนึ่งพบว่าการใช้ให้ 4% gelofusine ทางหลอดเลือดดำร่วมกับการให้ยาปฏิชีวนะสามารถลดการเกิดไตวายและลดอัตราตายในผู้ป่วยตับแข็งที่มีความเสี่ยงสูงได้ใกล้เคียงกับการให้ยาปฏิชีวนะร่วมกับการให้อัลบูมิน*

***วัตถุประสงค์**: เพื่อประเมินผลของการให้ 4% gelofusine ร่วมกับยาปฏิชีวนะ ceftriaxone ต่อการทำงานของไตและอัตราการเสียชีวิตในผู้ป่วยตับแข็งที่มีการติดเชื้อในช่องท้องแบบปฐมภูมิในกลุ่มที่มีความเสี่ยงสูง*

***วัสดุและวิธีการ**: ผู้ป่วยตับแข็งที่มีการติดเชื้อในช่องท้องแบบปฐมภูมิในกลุ่มที่มีความเสี่ยงสูงจำนวน 18 ราย ได้รับการรักษาด้วยการให้ยาปฏิชีวนะ ceftriazone ขนาด 2 กรัมต่อวันจนกว่าการติดเชื้อหายไปร่วมกับการให้ 4% gelofusine ขนาด 1.5 กรัมต่อน้ำหนักตัวหนึ่งกิโลกรัมในครั้งแรกและตามด้วย 4% gelofusine ขนาด 1.0 กรัมต่อน้ำหนักตัวหนึ่งกิโลกรัมในวันที่ 3 ของการรักษา ประเมินการทำงานของไตและอัตราการเสียชีวิตระหว่าง และหลังการรักษา*

***ผลการศึกษา**: ผู้ป่วย 5 ราย มีภาวะไตวายอยู่ก่อนแล้ว การติดเชื้อในช่องท้องหายผู้ป่วยส่วนใหญ่ (83.3%) ผู้ป่วย 3 ราย เกิดไตวายใน (16.7%) และผู้ป่วย 6 ราย เสียชีวิต (33.3%) อัตราการเสียชีวิตของผู้ป่วยที่หนึ่งเดือนหลังการรักษาเท่ากับ 33.3% ผู้ป่วยที่มีไตวายมีระดับของเรนินในพลาสมาสูงกว่าผู้ป่วยในกลุ่มไม่มีไตวาย แต่ไม่มีความสำคัญทางสถิติ*

***สรุป**: ในผู้ป่วยตับแข็งที่มีการติดเชื้อในช่องท้องแบบปฐมภูมิในกลุ่มที่มีความเสี่ยงสูง การรักษาด้วยการให้ 4% gelofusine ร่วมกับยาปฏิชีวนะ ลดอัตราการเกิดไตวายแต่ไม่ลดอัตราการเสียชีวิตของผู้ป่วยเมื่อเทียบกับการศึกษาก่อนหน้านี้ การศึกษาที่มีขนาดใหญ่กว่านี้น่าจะมีประโยชน์ในการประเมินผลของการรักษาต่อการทำงานของไต และอัตราการเสียชีวิตในผู้ป่วยกลุ่มนี้*