ORIGINAL RESEARCH ARTICLE   **Open Access**

High efficacy of low-dose albumin infusion in the prevention of paracentesis-induced circulatory dysfunction

Ayman Alsebaey* , Eman Rewisha and Imam Waked

Abstract

Background: Large-volume paracentesis (LVP) is a main pillar in treating patients with tense ascites. Without plasma expanders use, paracentesis-induced circulatory dysfunction (PICD) is a common complication with decreased survival. The aim was to compare low-dose albumin (2 g/L ascitic fluid removed $n = 85$) with standard-dose albumin (6 g/L ascitic fluid removed, $n = 25$) for prevention of PICD. Liver function tests, urea, creatinine, CBC, and abdominal ultrasonography were done. Plasma renin activity (PRA) was measured at baseline and on the 6th day post-LVP. The delta change (Δ) = day 6 variable minus baseline variable value. PICD was defined as increase in PRA of > 50% of the baseline value.

Results: Patients in low-dose albumin group were mainly Child B compared with Child C (85.9% vs. 52%; $p = 0.001$), underwent less paracentesis volume (9.78 ± 3.56 vs. 12.52 ± 3.6 L; $p = 0.001$), but had higher baseline PRA (859.62 ± 1151.34 vs. 165.93 ± 95.34 pg/mL; $p = 0.001$). In both groups, the PRA increased at day 6 compared with the baseline (1141.57 ± 1433.01 vs. 859.62 ± 1151.34 pg/mL; $p = 0.01$) and (192.21 ± 80.99 vs. 165.93 ± 95.34 pg/mL; $p = 0.01$) respectively. Both groups were comparable for Δ PRA (281.95 ± 851.4 vs. 26.28 ± 30.2 pg/mL; $p = 0.102$) and PRA percent increase (10.97 ± 30.77 vs. 12.57 ± 14.87; $p = 0.844$). They had comparable PICD incidence (24.7% vs. 12%; $p = 0.27$). Females were more liable for PICD occurrence than males (OR 2.91, 95% CI 1.125–7.547, $p = 0.028$) and so Child B patients than Child C (OR 8.4, 95% CI 1.072–65.767, $p = 0.043$).

Conclusion: Low-dose albumin infusion is comparable to the standard-dose albumin for the prevention of PICD.

Keywords: Large-volume paracentesis, Ascites, Albumin, Paracentesis-induced circulatory dysfunction, Plasma renin activity

Background

Liver cirrhosis is the final station of many liver diseases. Clinically, it may be compensated then after a variable period being decompensated. The development of ascites is the main sign of decompensation [1]. Actually, ascites develops in 50% of the patients within 10 years of liver cirrhosis diagnosis. Ascites is associated poor survival where 50% of the patients survive for 2–5 years [2].

Clinically, ascites is classified into 3 grades. The 1st and the 2nd one can be managed by salt restriction and diuretics, but the 3rd degree "tense" ascites is managed by large-volume paracentesis (LVP) followed by diuretics.

About 20% of the patients who were diuretic responder will be diuretic resistant [3, 4].

Refractory ascites is a condition that is seen in 10% of patients with ascites. It is due to resistance to diuretics "diuretic-resistance ascites" or contraindication for diuretics "diuretic-intractable ascites". Until now, the main arms for the treatment of patients with tense or refractory ascites is LVP or transjugular intrahepatic portosystemic shunt (TIPS). Liver transplantation is the best solution. In fact, TIPS is associated with decreased demand for paracentesis, for nutritional improvement, and may be for survival benefit though it is associated with increased risk of encephalopathy. So, LVP is still the first option especially that TIPS is not widely available [4, 5].

Paracentesis-induced circulatory dysfunction (PICD) is a complication of LVP that is less seen if paracentesis is less

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than 5 L. It is related to marked activation of the renin-angiotensin and sympathetic nervous systems over the levels before paracentesis. It is preventable by plasma expanders use especially human albumin (6–8 g/L ascitic fluid removed). PICD is associated with rapid re-accumulation of ascites, dilutional hyponatremia, hepatorenal syndrome, and decreased survival [6].

Albumin is not a simple plasma expander but has other advantages as detoxification of reactive oxygen and nitrogen species, endothelial stabilization and platelet anti-aggregation, and modulation of the immune and inflammatory responses [7]. The main drawback is that the drug is costly, so searching for alternatives is highly warranted [8].

This study aimed to compare low-dose albumin (2 g/L ascitic fluid removed) to standard-dose albumin (6 g/L ascitic fluid removed) for the prevention of PICD.

Methods

In our previous study [8], we compared terlipressin (3 mg IV), hydroxyethyl starch (HES 130/0.4; 8 g/L ascitic fluid removed), oral midodrine (5–10 mg daily), low-dose albumin (2 g/L ascitic fluid removed), and standard-dose albumin (6 g/L ascitic fluid removed) for PICD prevention. All groups were equal for PICD development. In this study, we could increase the number of patients in low-dose albumin group.

This study was conducted in National Liver Institute hospitals, hepatology, and gastroenterology department, Menoufia University. Prior institutional review board approval was acquired, and then an informed consent was obtained from all enrolled patients.

Patients who were requiring LVP for tense ascites (*n* = 110) were included in the study. Liver cirrhosis was diagnosed according to the clinical, laboratory, and abdominal ultrasonography findings [9].

Patients with the following criteria were included: tense ascites requiring LVP, age 18–70 years old, absence of cardiac disease, respiratory disease, hepatic encephalopathy, sepsis, spontaneous bacterial peritonitis, renal impairment (serum creatinine > 1.5 mg/dL), and gastrointestinal hemorrhage within 7 days before the study. All patients were on a low-sodium diet (34 mmol/day) for at least 7 days outpatient before inclusion in the study.

On day 0, a baseline workup, including body weight, mean arterial pressure (MAP), heart rate, electrocardiogram, liver tests (bilirubin, albumin, AST, ALT, alkaline phosphatase), and renal function tests (urea and creatinine), were conducted. Blood samples were collected after an overnight fast and bed rest for at least 30 min in the supine position for measuring PRA. Blood samples were put into chilled ethylenediaminetetraacetic acid tubes, centrifuged at 2500 rpm for 10 min at − 3 °C, and stored at − 20 °C. Total paracentesis was then done under local anesthesia and strict aseptic conditions.

Patients were categorized into 2 groups: low-dose albumin (2 g/L ascitic fluid removed; *n* = 85) and standard-dose albumin (6 g/L ascitic fluid removed; *n* = 25). Human albumin (20%; infusion solution; DRK-Blutspendedienst NSTOB 31830 Springe; each 1000 ml containing 200 g of human albumin) was used. Fifty percent of the dose was given within 2 h and the remainder 6 h after the procedure if more than 150 mL was infused to avoid pulmonary edema.

From day 1 to day 5, the patients were monitored daily for body weight, daily urine output volume, blood pressure, heart rate, and development of complications. On the day of hospital discharge (day 6), blood pressure, heart rate, and weight were recorded. Electrocardiogram, renal, and liver function tests were done, and blood was collected for PRA. Changes of the effective arterial blood volume were evaluated by measuring plasma rennin activity (PRA) on the day of paracentesis (day 0; baseline) and on the day of hospital discharge (day 6).

The primary end point was taken as development of PICD that was defined as an increase in PRA of > 50% of the baseline value [10]. PRA was laboratory measured in accord with Alsebaey et al [8].

Statistical analysis

Data was statistically analyzed using IBM® SPSS® Statistics® version 21 for Windows (IBM Corporation, Armonk, New York, USA). Data are expressed as mean ± standard deviation for parametric data, number with column percentage for nominal data, and the range for non-parametric data. All *p* values are two tailed, with values < 0.05 considered statistically significant. Comparisons between two groups were performed using the Student's *t* test for parametric data, and Mann-Whitney test for nonparametric data. Comparisons of the variables treatment induced change in the same group were performed using the paired *t* test for parametric data and Wilcoxon signed ranks test for nonparametric data. Chi-squared test (χ^2) and Fisher exact test for categorical data analysis. Univariate and multivariate binary logistic regression was done for detecting the predictors of PICD.

Results

Table 1 shows the baseline data in both groups. There was a statistically significant difference (*p* < 0.05) between both groups as regards the Child Pugh class, paracentesis volume, baseline serum albumin, and baseline PRA.

Patients who underwent low-dose albumin infusion post-paracentesis were mainly Child Pugh class B in contrast to patients in the other group (85.9% vs. 52%; *p* = 0.001), underwent less average paracentesis volume (9.78 ± 3.56 (7–25 L) vs. 12.52 ± 3.6 (6–20 L); *p* = 0.001), less baseline serum albumin (2.20 ± 0.36 vs. 2.55 ± 0.6 g/dL; *p* = 0.002), but higher baseline PRA (859.62 ± 1151.34 vs. 165.93 ± 95.34 pg/mL; *p* = 0.001).

Table 1 Comparison of the baseline parameters in both groups

		Low-dose albumin	Standard-dose albumin	p
		N = 85	N = 25	
Age (years)		53.19 ± 8.55	51.60 ± 6.84	0.397
Sex	Male	50 (58.8%)	9 (36%)	0.067
	Female	35 (41.2%)	16 (64%)	
Etiology	HCV	80 (93%)	22 (91.7%)	1
	Non-HCV	6 (7%)	2 (8.3%)	
Child Pugh class	Child B	73 (85.9%)	13 (52%)	0.001
	Child C	12 (14.1%)	12 (48%)	
PICD	None	64 (75.3%)	22 (88%)	0.27
	PICD	21 (24.7%)	3 (12%)	
Weight, kg		90.56 ± 11.26	87.08 ± 14.18	0.252
MAP, mmHg		78.98 ± 6.40	77.58 ± 5.81	0.358
Heart rate, beat/minute		83.70 ± 13.73	83.12 ± 5.24	0.84
Paracentesis, L		9.78 ± 3.56	12.52 ± 3.60	0.001
Total bilirubin, mg/dL		3.04 ± 2.65	2.78 ± 1.59	0.643
Total protein, g/dL		6.38 ± 0.93	6.33 ± 1.21	0.836
Albumin, g/dL		2.20 ± 0.36	2.55 ± 0.60	0.002#
AST, U/L		53.48 ± 26.78	72.32 ± 48.92	0.106#
ALT, U/L		35.48 ± 27.80	35.84 ± 24.11	0.954
ALP, U/L		104.21 ± 132.88	119.24 ± 103.15	0.604
GGT, U/L		47.66 ± 46.11	52.95 ± 68.15	0.66
Hemoglobin, g/dL		10.36 ± 1.32	10.12 ± 1.98	0.319#
WBCs, 10^9/L		6.90 ± 9.27	4.98 ± 2.55	0.309
Platelets, 10^9/L		82.14 ± 33.32	83.60 ± 38.47	0.853
INR		1.62 ± 0.51	1.55 ± 0.28	0.495
Urea, mg/dL		55.35 ± 30.48	38.16 ± 17.07	0.003#
Creatinine, mg/dL		0.95 ± 0.27	0.85 ± 0.36	0.103#
Sodium, mmol/L		123.25 ± 13.85	128.16 ± 6.03	0.088
Potassium, mmol/L		4.28 ± 0.69	4.20 ± 0.58	0.636
Child Pugh score		10.36 ± 1.26	9.88 ± 1.56	0.113
MELD		15.24 ± 4.41	15.28 ± 4.11	0.964
MELD Na		22.88 ± 4.12	21.88 ± 4.02	0.285
PRA, pg/mL		859.62 ± 1151.34	165.93 ± 95.34	0.001#

PICD paracentesis-induced circulatory dysfunction, *MAP* mean arterial pressure, *PRA* plasma renin activity, *HCV* hepatitis C virus, *MELD* model for end-stage liver disease
#Mann–Whitney *U* test

The other parameters did not show statistically significant difference ($p > 0.05$), namely age, sex, weight, MAP, heart rate, serum bilirubin, serum total protein, AST, ALT, ALP, GGT, hemoglobin, WBCs, platelets, INR, blood urea, serum creatinine, sodium, potassium, MELD, and MELD Na score.

The delta change (Δ) = day 6 variable value minus baseline variable value. Positive delta means higher day 6 value than baseline and vice versa. There was a statistically significant difference ($p < 0.05$) between both groups as regards the Δ weight and Δ blood urea (Table 2). Patients

underwent low-dose albumin infusion post-paracentesis had less drop in the weight (− 4.35 ± 7.02 vs. − 10.64 ± 3.67 kg; $p = 0.001$) but higher blood urea increase (14.96 ± 23.84 vs. 3.72 ± 10.62 mg/dL; $p = 0.005$).

Delta MAP, heart rate, serum bilirubin, serum total protein, serum albumin, AST, ALT, ALP, GGT, hemoglobin, WBCs, platelets, INR, serum creatinine, sodium, potassium, model of end-stage liver disease (MELD), and MELD Na score did not show a statistically significant difference ($p > 0.05$) between both groups.

Table 2 Comparison of treatment induced changes in both groups

	Low-dose albumin N = 85	Standard-dose albumin N = 25	p
Δ Weight, kg	− 4.35 ± 7.02	− 10.64 ± 3.67	0.001#
Δ MAP, mmHg	− 1.59 ± 9.29	− 1.19 ± 6.09	0.699#
Δ Heart rate, beat/minute	2.07 ± 14.14	0.80 ± 3.18	0.523#
Δ Total bilirubin, mg/dL	0.15 ± 0.89	0.12 ± 0.59	0.756#
Δ Total protein, g/dL	− 0.12 ± 0.49	− 0.28 ± 0.85	0.249
Δ Albumin, g/dL	− 0.01 ± 0.19	2.35 ± 11.56	0.65#
Δ AST, U/L	− 0.95 ± 24.65	0.80 ± 25.02	0.756
Δ ALT, U/L	− 2.34 ± 24.98	2.44 ± 12.10	0.358
Δ ALP, U/L	− 12.06 ± 114.57	− 31.12 ± 106.93	0.46
Δ GGT, U/L	− 1.72 ± 20.57	− 7.86 ± 72.38	0.486
Δ Urea, mg/dL	14.96 ± 23.84	3.72 ± 10.62	0.005#
Δ Creatinine, mg/dL	0.14 ± 0.35	0.06 ± 0.29	0.348#
Δ Sodium, mmol/L	−1.84 ± 17.39	− 2.72 ± 1.43	0.8
Δ Potassium, mmol/L	0.07 ± 0.69	− 0.14 ± 0.64	0.166
Δ MELD	0.79 ± 3.46	0.12 ± 1.59	0.145#
Δ PRA, pg/mL	281.95 ± 851.4	26.28 ± 30.2	0.102#
PRA percent increase	10.97 ± 30.77	12.57 ± 14.87	0.844#

Δ indicates day 6 values to day 1 value

MAP mean arterial pressure, *PRA* plasma renin activity

#Mann–Whitney *U* test

Tables 1 and 2 and Figs. 1 and 2 showed the PICD studied parameters. Patients in the low-dose albumin group had higher baseline PRA (859.62 ± 1151.34 vs. 165.93 ± 95.34 pg/mL; *p* = 0.001) (Table 1). In both low-dose and standard-dose albumin groups, the PRA increased at day 6 compared with the baseline (1141.57 ± 1433.01 vs. 859.62 ± 1151.34 pg/mL; *p* = 0.01) and (192.21 ± 80.99 vs. 165.93 ± 95.34 pg/mL; *p* = 0.01) respectively (Fig. 1). Both the low-dose and standard-dose albumin groups were comparable for Δ PRA (281.95 ± 851.4 vs. 26.28 ± 30.2 pg/mL; *p* = 0.102) (Table 2, Fig. 1), and PRA percent increase (10.97 ± 30.77 vs. 12.57 ± 14.87; *p* = 0.844) respectively (Fig. 1). By application of the PICD definition [10], both low-dose and standard-dose albumin groups had comparable PICD incidence (24.7% vs. 12%; *p* = 0.27) (Fig. 2).

The univariate binary regression analysis (Table 3) showed that females were more liable for PICD occurrence than males (OR 2.91, 95% CI 1.125–7.547, *p* = 0.028) and so Child Pugh class B patients than class C (OR 8.4, 95% CI: 1.072–65.767, *p* = 0.043). The multivariate binary regression found also that females were more liable for PICD occurrence than males (OR 3.07, 95% CI: 1.155–8.162, *p* = 0.025) and so Child Pugh class B patients than class C (OR 8.92, 95% CI: 1.120–71.118, *p* = 0.039).

On comparison of the two current studies groups with previously published data [8] as shown in Table 4 and
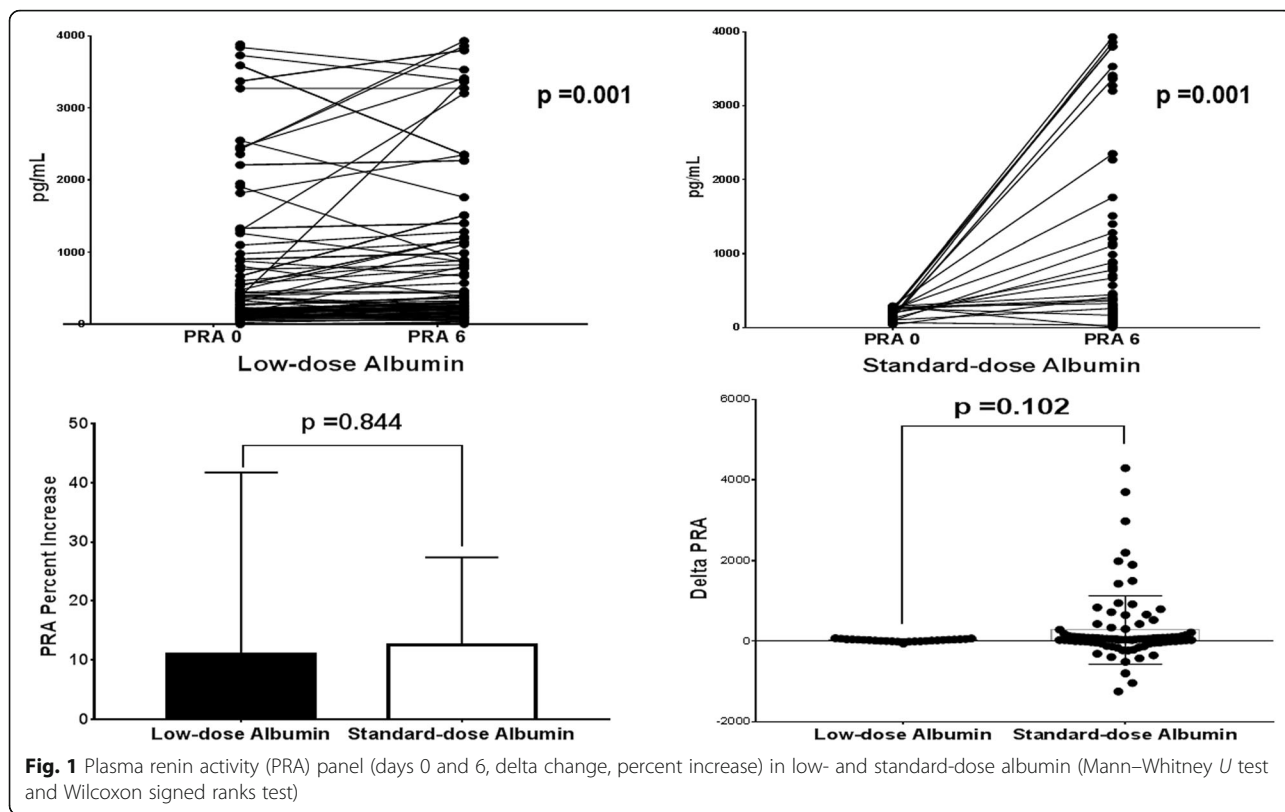
Fig. 3, all groups namely terlipressin, HES 130/0.4, midodrine, low-dose albumin, and standard-dose albumin were equal in the prevention of PICD (*p* > 0.05).

Discussion

The main concept of PICD pathogenesis is circulatory disturbance that develops after LVP if plasma expanders are not used. Immediately after LVP, there is decreased abdominal pressure, increased venous return, increased cardiac output, and suppression of the renin-angiotensin-sympathetic system. After 12 h, if no plasma expanders are used, the opposite occurs with marked activation of the renin-angiotensin-sympathetic system with reduced cardiac output. PICD may not be mere circulatory derangement [6]. In fact, Carl et al [11] in a small study (*n* = 10) hypothesized that LVP-induced hypotension increased bacterial translocation, innate immune activation that is responsible of vasodilation and subsequent PICD development.

PICD development is unrelated to the paracentesis flow rate [12]. SerSté et al [13] accused Beta blockers in the development of PICD in a small number study (*n* = 10). PICD can be prevented by either plasma expanders or finding other solutions to avoid or replace LVP which is the accused factor.

Regarding avoiding LVP, TIPS is a good solution since it modifies the pathogenesis of ascites and improves the quality of life and survival. Unfortunately, the increased

Fig. 1 Plasma renin activity (PRA) panel (days 0 and 6, delta change, percent increase) in low- and standard-dose albumin (Mann–Whitney *U* test and Wilcoxon signed ranks test)

incidence of hepatic encephalopathy is a drawback [4]. Permanent-tunneled peritoneal catheter is a new modality to avoid LVP [14]. It is not associated with renal impairment but further studies are needed. Alfa pump is another new modality "low flow pump system" for the treatment of refractory ascites [15–17]. It pumps the ascitic fluid through a valve to the urinary bladder and gets out by urination. It is considered continuous low-volume paracentesis. It decreased the ascites grade and the LVP times [15, 16]. Bureau et al [17] compared alfa pump to standard of care LVP with albumin replacement. Patients who underwent alfa pump had a marked decreased need for LVP, improved quality of life, and nutritional status but unfortunately increased the adverse effects especially early acute kidney injury. Both groups had the same survival. The enthusiasm for alfa pump will fades with the small number study ($n = 10$) by Solà et al [18]. They followed up the patients for 1 year with measure of the glomerular filtration rate by isotopes, blood pressure, and activity of vasoconstrictor
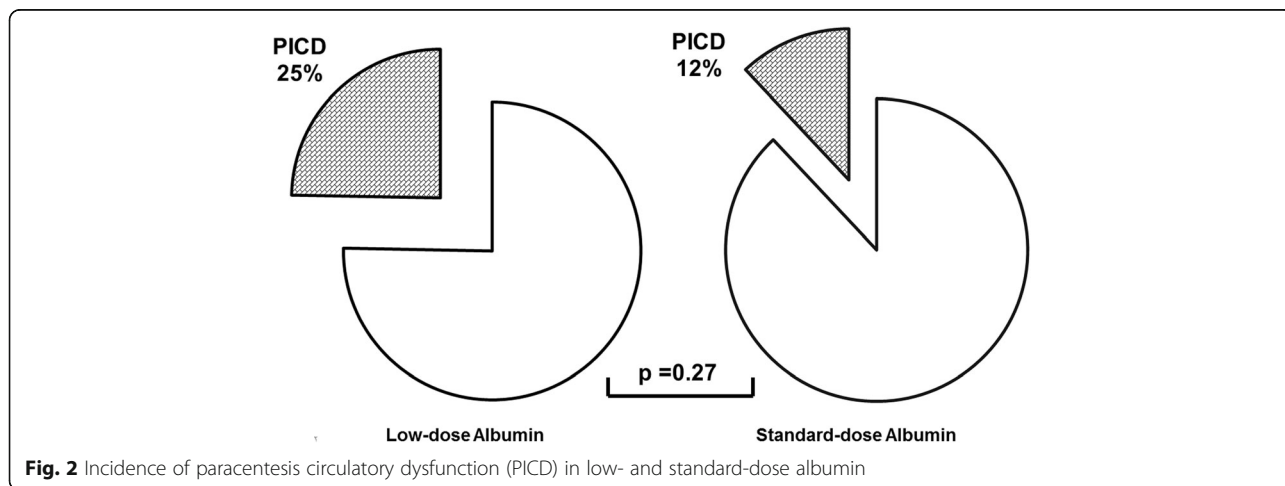

Fig. 2 Incidence of paracentesis circulatory dysfunction (PICD) in low- and standard-dose albumin

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Table 3 Univariate and multivariate analysis of predictors of PICD occurrence

	Univariate				Multivariate			
	B	p	OR	95% CI	B	p	OR	95% CI
Age	− 0.01	0.737	0.99	0.937–1.047				
Females	1.07	0.028	2.91	1.125–7.547	1.12	0.025	3.07	1.155–8.162
Child Pugh B	2.13	0.043	8.40	1.072–65.767	2.19	0.039	8.92	1.120–71.118
MAP, mmHg	0.03	0.505	1.03	0.940–1.133				
Low-dose albumin	0.88	0.187	2.41	0.654–8.857				
Paracentesis liters	0.00	0.970	1.00	0.883–1.127				
Total bilirubin	− 0.06	0.545	0.94	0.768–1.149				
Albumin	0.41	0.408	1.51	0.567–4.038				
Urea	0.01	0.238	1.01	0.994–1.023				
Creatinine	0.28	0.725	1.32	0.281–6.216				
Sodium	− 0.03	0.183	0.97	0.937–1.012				
MELD	− 0.01	0.919	0.99	0.895–1.105				
MELD Na	0.00	0.942	1.00	0.899–1.122				

MAP mean arterial pressure, *OR* odds ratio, *CI* confidence interval, *MELD* model for end-stage liver disease, *Na* sodium

systems. The patients had significant decreased glomerular filtration rate at the 6th month and marked increase of PRA and norepinephrine concentration, with increased incidence of acute kidney injury. These features actually mimic PICD.

Tan et al [19] studied subtotal LVP not exceeding 8 L with using standard-dose albumin (6 g/L ascitic fluid removed; $n = 57$) as a method for PICD prevention. They used plasma active renin instead of PRA. PICD was detected in 40.3% of patients. The MAP decreased at day 6 compared with the baseline in patients with and without PICD. Though they had comparable baseline and day 6, creatinine with no renal impairment was noted. These patients were followed up 24 months. They had comparable serial creatinine values; same risk of hospitalization, spontaneous bacterial peritonitis, other infections, or gastrointestinal bleeding; and finally same survival.

IV albumin infusion (6–8 g/L ascitic fluid removed) is the standard of care plasma expander to prevent PICD. But it is associated with increased cost, so finding alternatives is warranted. Various drugs were studied like terlipressin [8, 20–23], noradrenaline [20, 24], midodrine [8, 25–27], synthetic colloids [8, 28–34], and saline [35, 36]. Our previous study [8] is the first study to our knowledge that did head-to-head

drug comparison. All previous studies compared the used drug, e.g., terlipressin to the standard of care IV albumin. In our previous study, we compared terlipressin, midodrine, HES 130/0.4, and low-dose albumin (2 g/L ascitic fluid removed) to the standard-dose albumin (6 g/L ascitic fluid removed). The incidence of PICD was comparable in all groups, suggesting that albumin alternatives could be used.

Why returning back to albumin? The study of Carl et al [11] suggested that there are bacterial translocation and innate immune activation that play a role in PICD development. Since albumin has antioxidant, immunomodulatory effect in addition to increased oncotic pressure [37], it will be the preferred drug in such condition. To skip the high cost of albumin, using low doses may be of benefit.

Alessandria et al [38] was the first researcher who suggested the use of low-dose albumin. She compared low-dose albumin (4 g/L ascitic fluid removed; $n = 35$) with standard-dose albumin (8 g/L ascitic fluid removed; $n = 35$). Both groups were comparable for PICD development (14% vs 20%) respectively and 6-month survival or recurrence of ascites. The second study was conducted by Alsebaey et al [8]. One arm was low-dose albumin (2 g/L ascitic fluid removed; $n = 25$) which is the lowest tested dose compared with other studies [38, 39]. The

Table 4 Comparison of different treatment protocols for the PICD prevention

		Terlipressin	HES 130/0.4	Midodrine	Low-dose albumin	Standard-dose albumin	p
		N (%)	N (%)	N (%)	N (%)	N (%)	
PICD	None	23 (92%)	23 (92%)	20 (80%)	64 (75.3%)	22 (88%)	0.153
	PICD	2 (8%)	2 (8%)	5 (20%)	21 (24.7%)	3 (12%)	

PICD paracentesis-induced circulatory dysfunction

Fig. 3 Incidence of paracentesis circulatory dysfunction (PICD) in different groups, namely terlipressin, HES 130/0.4, midodrine, and low- and standard-dose albumin
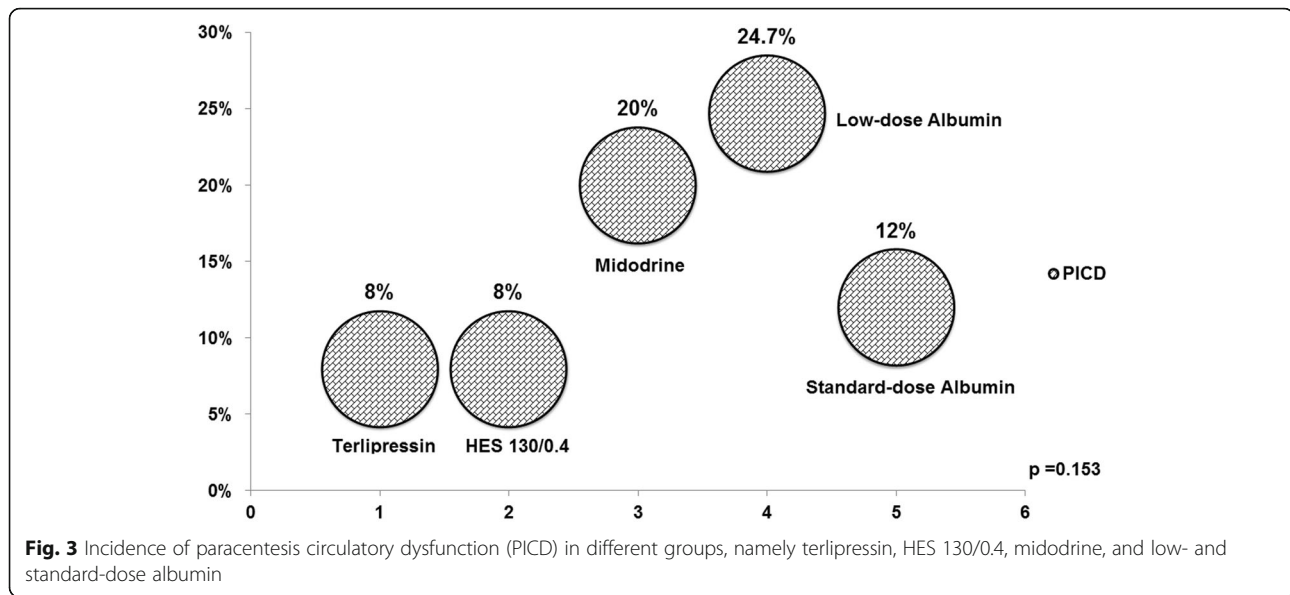
PICD incidence in low-dose albumin was comparable to standard-dose albumin (6 g/L ascitic fluid removed; $n = 35$), HES 130/0.4, midodrine, and terlipressin. The third study was conducted by Hussain et al [39] on the utility of low-dose albumin (4 g/L ascitic fluid removed) on the prevention of paracentesis induced renal impairment. Actually, he did not measure PRA; he just followed up serum creatinine and sodium. Furthermore, he did not have arm of standard-dose albumin. He compared the utility of low-dose albumin in the prevention of renal impairment in patients who underwent low-volume paracentesis (6.2 ± 1 L) and large-volume paracentesis (10.4 ± 1.5 L). Few patients developed renal impairment (4.62% vs. 6.45%) respectively.

In the current study, only blood urea increased from baseline to the 6th day especially in the low-dose albumin compared with the standard-dose albumin in contrast to creatinine which was not affected. The PRA increased in both groups, but the delta change and the percent increase were comparable in both groups. In addition, the PICD development was comparable in both groups. Females and Child Pugh class B patients were more liable for PICD development. When we compared the current two arms with the old arms in our previous study [8], the incidence of PICD was comparable in the five groups, namely terlipressin, HES 130/0.4, low-dose albumin (2 g/L ascitic fluid removed), and the standard-dose albumin (6 g/L ascitic fluid removed).

The limitations of the current study are being single center experience, have relative small number of patients, and have absence of longitudinal follow-up to calculate the incidence of renal impairment, infections, bleeding, and importantly the survival.

Conclusion

Low-dose albumin infusion is comparable to the standard-dose albumin for the prevention of PICD. Furthermore, it is equivalent to terlipressin, midodrine, and HES 130/0.4 for PICD prevention.

Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate
It is approved by National Liver Institute IRB 0088/2014. Informed written consent was signed by all patients.

Consent for publication
Not applicable

Competing interests
Imam Waked is an investigator and/or speaker for Abbvie, Gilead Sciences, Janssen, Marcyrl, Onxio, and Pharco. The rest of the authors declare that they have no competing interests.

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