Midodrine in Liver Cirrhosis With Ascites: A **Systematic Review and Meta-Analysis**

Dhan B. Shrestha 1 , Pravash Budhathok
i 2 , Yub Raj Sedhai 5 , Ram Kaji Baniya
 4 , Pearlbiga Karki 5 , Pinky Jha 5 , Gaurab Mainali
 5 , Roshan Acharya 6,7 , Amik Sodhi
 8 , Dipen Kadaria 9

Review began 05/28/2022 Review ended 07/20/2022 ublished 07/30/2023

© Copyright 2022 Shrestha et al. This is an open access Shrestha et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ent of Internal Medicine, Mount Sinai Hospital, Chicago, USA 2. Department of Internal Medicine, 1. Depar Bronxcare Health System, New York, USA 3. Department of Internal Medicine, Virginia Commonwealth University Bronkzare Health System, New York, USA 3. Department of internal Medicine, Virgina Lommonwealth University School of Medicine, Richmond, USA 4. Department of Internal Medicine, Our Lady of Lake Regional Medical Centre, Louisiana, USA 5. Department of Internal Medicine, Nepalese Army Institute of Health Sciences, Kathmandu, NPL 6. Internal Medicine, Cape Fear Valley Hospital, Fayetteville, USA 7. Internal Medicine, Campbell University School of Osteopathic Medicine, Fayetteville, USA 8. Department of Fulmonary, Critical Care, and Sleep Medicine, University of Tennessee, Memphis, USA 9. Department of Internal Medicine, University of Tennessee, Memphis, USA

Corres onding author: Dhan B. Shrestha, medhan75@gmail.com

Abstract

Ascites is the most common complication of liver cirrhosis. Midodrine is a vasoconstrictor that improve splanchnic and systemic hemodynamics, reduces ascites, and improves clinical outcomes. Here, we aimed to examine the role of midodrine in cirrhosis-related ascites.

Scopus, Embase, PubMed, and PubMed Central databases were searched for relevant randomized controlled trials comparing midodrine with other interventions in patients with cirrhotic ascites on November 25, 2020, using appropriate keywords like "midodrine", "ascitic cirrhosis", "peritoneal paracentesis" and suitable Boolean operators: Odds ratio (OR) and mean difference (MD) were used to analyze pool data as appropriate with a 95% confident interval (CI).

A total of 14 studies were included in our analysis including 1199 patients. The addition of midodrine resulted in statistically significant improvement in mean arterial pressure (MAP) (MD, 3.95 mmHg; 95% CI, 1.53-6.36) and MELD (Model for End-Stage Liver Disease) score (MD, -1.27; 95% CI, -2.49 to -0.04) compare last obsolution medical treatment (SMT). There was also a significant improvement in plasma renin activity and plasma aldosterone concentration. However, there was no significant improvement in mortality or serum creatinine compared to SMT. In addition, there was no statistically significant improvement in MAP, plasma nin activity plasma aldos one concentration. MELD score, overall mortality, and paracentesis-induced circulatory dysfunction comparing midodrine with albumin.

Midodrine alone leads to significant improvement in various clinical parameters in patients with cirrhotic ascites compared to standard medical care. At the same time, it was found to be non-inferior to albumin. Therefore, further well-designed studies need to be carried out on midodrine in addition to albumin for optimal clinical benefits among patients with ascites due to cirrhosis.

Categories: Internal Medicine, Gastroenterology Keywords: meta-analysis, systematic review, ascites, cirrhosis, albumin, midodrine

Introduction And Background

Ascites is one of the most common and serious complications of liver cirrhosis [1]. Ascites is managed with diuretics and sodium restriction. Ascites that does not reduce or that occurs shortly after therapeu paracentesis despite sodium restriction and diuretic treatment is called refractory ascites [2]. Therapeutic paracentesis, combined with the expansion of plasma volume using albumin, is an effective and safe procedure with fewer risks that directic therapy in such cases [1]. Albumin, however, is expensive and, may have some risk of disease transmission; its use is thus controversial in some countries [1,3,4]. Peripheral arterial vasodilation has been hypothesized to be the critical factor in the pathogenesis of functional renal abnormalities in patients with cirrhosis [5]. Vasoconstrictor administration may decrease arteriolar vasodilation caused by paracentesis and prevent complications associated with a decrease in the effective vascuminor cased of paracterists and pre-rate on practices associated with a decreater in the electric arterial blood volume. Middenine, an alpha-ra gonist directly acting on peripheral alpha-receptors, is a vasoconstrictor and is available as a cheap oral formulation. It has been commonly used to treat orthostatic hypotension and multiple secondary hypotensive disorders [6-8]. Recently, a single-dose administration of midofrine has been shown to substantially improve the systemic and real hemodynamics of ascites in non-azotemic cirrhotic patients [7]. However, clinical trials evaluating Midodrine have provided inconclusive findings in patients with liver cirrhosis-related ascites, irrespective of the refractory status of the ascites [9].

ed to conduct a systematic review and meta-analysis to assess the effectiveness of midodrine in reducing mortality, improving response rates in patients with ascitic cirrhosis undergoing peritoneal sis/drainage, asses ent of MELD (Model For End-Stage Liver Disease), plasma renin, aldoster and creatinine

Review

Methods

Protoco

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was followed to ic review and meta-analysis and is registered in PROSPERO (CRD42020222872) [1

We included randomized controlled trials comparing midodrine with control intervention (e.g., placebo, sodium restriction, diuretic treatment, and therapeutic paracentesis) or an active intervention (e.g., different drug) in patients with cirrhotic ascites; and complete data for at least one primary end-point was reported. Studies like editorials, commentary, viewpoint, case reports and series, observational studies, and curve source in curve and curve and commentary, receiption and curve source source and curve and curve source and curve source and curve source and curve an

Search Strategy

Scopus, Embase, PubMed, and PubMed Central were used to search relevant articles till November 25, 2020, using appropriate keywords like "midodrine", "ascitic cirrhosis", and "peritoneal paracentesis," and suitable Boolean operators. The detailed search strategy is mentioned in the supplementary file

Study Selection

Two reviewers (PI and GM) independently screened the title and abstract of imported studies, and any arising conflict was solved by the third reviewer (PK). A full-text review was done independently by PI and PK. Data were extracted for both quantitative and qualitative synthesis. The conflicts were resolved by taking the third reviewer's opinion (GM). All the screening was done with the help of Covidence [11].

Data Extraction

A standardized form was designed in Microsoft Word to extract pertinent data, including study authors study details, quality, and endpoints. The endpoints for meta-analysis were the effect of midodrine on short-term mortality within the first three months, paracentesis-induced circulatory dysfunction, mean arterial pressure, MELD scores, serum creatinine, plasma renin, and aldosterone in cirrhotic ascites [12].

How to cite this article

Shrestha D B, Budhathoki P, Sedhai Y, et al. (July 30, 2022) Midodrine in Liver Cirrhosis With Ascites: A Systematic Review and Meta-Analysis. Cureus 14(7): e27483. DOI 10.7759/cureus.27483

Study Quality

The quality of individual articles was evaluated using the Cochrane ROB (Risk of Bias) 2.0 for RCTs [15]. The risk of bias was assessed (Figure 1). Two of the authors independently assessed the design of each study, and the number of patients in outcomes including short-term mortality, paracentesis-induced circulatory dysfunction, serum creatinine, plasma renin, plasma aldosterone, and MELD scores. Third-person (among authors) resolved the disagreement.



FIGURE 1: Risk of Bias assessment of included RCTs Included studies are reference nos. [1, 3, 4, 6-8, 14-22]

Data Analysis

Data were analyzed using RevMan v5.4 (https://training.cochrane.org/). Odds ratio (OR) was used for outcomes like short-term mortality and paracentesis-induced circulatory dysfunction (PICD). Heterogenetic was measured by the 7 test among the included studies. For data synthesis, a qualitative approach was planned. The handling of data and combining results of the studies was done using OR and using the random or fixed effect model based on heterogenetics. We analyzed the mean difference among the two groups for mean arterial pressure, MELD scores, plasma renin, plasma aldosterone, and serum creatinine level.

Sensitivity Analysis

Subgroup analysis was done within the respective outcomes contrasting albumin-based control and other treatments as a control.

Publication Bias

Publication bias of the included studies was assessed and presented using Funnel plots.

Results

We identified a total of 865 studies through a thorough database search. A total of 318 duplicates were removed, and we screened the title and abstracts of 547 studies. After excluding 497 studies, we assessed the full text of 50 studies, and 30 studies were excluded for definite reasons (Figure 2). Therefore, 15 remaining studies were included in our qualitative analysis.



FIGURE 2: PRISMA Flow Diagram

PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Narrative summary

Qualitative Analysis

We included 15 studies in our qualitative analysis presented in Table 1. Basic details of included studies are shown in the supplementary file. Narrative summary of included studies is shown in Table 1 [1,5,4,6-8,14-22].

Study ID	Particulars	Intervention group	Comparator group
	Year	2013	
	Study design	RCT	
	Total participants	50	
	Description	Oral midodrine (5–10 mg three times daily)	Standard-dose albumin (6 g/l ascetic fluid removed) Others intravenous terlipressin (3 mg), intravenous Hydroxyethyl Starch(HES) (8 g/l ascetic fluid removed), Low-dose albumin (2 g/l ascetic fluid removed)
	Population characteristics		
	Participants	25	25
	Male (number/total)	18/25	9/25
	Female (number/total)	7/25	16/25
	Weight (Kg)	82.04 ± 10.49	87.08 ± 14.18
	Baseline Values		
	MELD score	13.68 ± 4.17	15.28 ± 4.11
	MAP(mmHg)	77.44 ± 6.54	77.58 ± 5.81
Alsebaey et	Serum creatinine(mg/dL)	0.92 ± 0.37	0.85 ±0.36
al. (2013) Plasma renin (mU/ml)	162.38 ± 91.00	165.93± 95.34	
	Aldosterone(pg/ml)	797.66 ±755.07	837.50±899.48
	Outcome		
	Change in Values on Day 6		
	ΔMAP (mmHg)	0.00 ± 7.65	- 1.19 ± 6.09
	ΔMELD score	0.04 ± 2.24	0.12 ± 1.59
	ΔSerum creatinine(mg/dL)	0.02 ± 0.23	0.06 ±0.29
	ΔUrine output (ml/min)	292.00 ± 400.96	468.00± 324
	ΔPRA (µU/ml)	30.75 ± 85.07	26.28 ± 30.20
	∆Aldosterone(pg/ml)	-26.60±633.89	9.84±828.46
	Risk of development of paracentesis-induced circulatory dysfunction PICD		
	Positive(number/total)	5/25	3/25
	Negative(number/total)	20/25	22/25
	Year	2008	
	Study design	RCT	
	Total participants	24	
	Description	Midodrine (12.5 mg post- paracentesis every 8 h for 2 days, six doses each) after the end of paracentesis	Albumin(8 g/L of removed ascites) with placebo pills

	Population characteristics		
	Participants	11	13
	Male(number/total)	7/11	9/13
	Female(number/total)	4/11	4/13
	AGE mean	52 (48;61)	60 (50;63)
	Weight (kg)	67±11	69±13
	Baseline Values		
	Volume of ascites removed (I)	7 (5.7; 10)	5.5(5;7.7)
	MELD score	11(8:14)	11 (6:17)
Appenrodt	MAP (mmHa)	77 (70:79)	76 (63:82)
et al.	Conum exceliping (mg/dl.)	0.08 (0.79:1.16)	1 (0.99:1.12)
(2008)	Serum creatinine(mg/dE)	0.50 (0.76, 1.10)	
	Creatinine clearance(ml/min)	66 (25.5;80)	63.5 (39.8;85.3)
	S-Na(mmol/L)	131 (128;133)	129 (125;131)
	Plasma renin (mU/ml)	677.5 (179.7;2016.3)	385(173;2529)
	PAC (pg/mL)	858 (743.6;1446	911(437;1816.5)
	Outcome		
	Median values with IQR On day	y 6	
	MAP (mmHg)	80 (62;91)	81 (74;83)
	Serum creatinine(mg/dL)	0.93 (0.86;1.13)	0.98 (0.89;1.12)
	Creatinine clearance(ml/min)	47 (27;85)	44.5 (35.5;72.3)
	Plasma renin (mU/ml)	1337.5 (500:3363)	402.0(145.5:1889)
	PAC (pa/ml.)	1266 (1043:2141)	992(776.0: 1546.5)
	Paragantagia laducad	1200 (1040,2141)	332(110.0, 1040.0)
	Circulatory Dysfunction (PICD)(number/total)	6/11 (60%)	4/13 (31%)
	Renal impairment(number/total)	2/11 (20%)	0
	Year	2018	
	Study design	RCT	
	Total participants	75	
	Description	T1 (2 days Midodrine) Midodrine 12.5 mg every 8 h for 2 days after LVP. T2(30days midodrine) Midodrine 12.5 mg every 8 h for 30 days after LVP	Regular dose of alburnin (8 g for each liter of removed ascitic fluid) immediately after LVP
	Population characteristics		
	Participants	T1=25; T2=25	25
	Male(number/total)	T1=17/25, T2= 18/25	18/25
	Female(number/total)	T1=8/25, T2=7/25	7/25
	Age	T1=51.36±11.68,T2= 50.48±7.93	48.80±10.25
	weight(kg)	T1= 80.04±8.75,T2=	70.84+0.06
		00.1010.20	10.0420.00
	Baseline Values	00.1010.20	10.0123.00
	Baseline Values Volume of ascites removed(I)	T1=5.80±0.92,T2= 6.13±0.81	5.66±0.83
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I)	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49	5.66±0.83 130.88±3.06
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20	5.66±0.83 130.88±3.06 1.24±0.17
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L)	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=2.6.84±8.68,T2= 23.28±6.92	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L)	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=2.6.84±8.68,T2= 23.28±6.23	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27
Yosry et al. (2018)	Baseline Values Volume of ascites removed() Na (mEq/l) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR)	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27
Yosry et al. (2018)	Baseline Values Volume of ascites removed() Na (mEq/l) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=2.6.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.36±0.32,T2= 1.24±0.28	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= T1=8.2±5.06,T2= T1=1.35±0.32,T2= 1.24±0.28 T1= 68,73±20.76, T2=	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.3±2.96
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 68.73±20.76, T2= 77.03±20.93	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance on Day 30	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 68.73±20.76, T2= 77.03±20.93	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance on Day 30	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 68.73±20.76, T2= 77.03±20.93 T1= 80.87±4.41,T2=	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance on Day 30 MAP	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 68.73±20.76, T2= 77.03±20.93 T1= 80.87±4.41,T2= 76.45±6.32	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance on Day 30 MAP Serum creatinine	T1=5.80±0.92,T2= 6.13±0.81 T1=52.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.245.06,T2= 76.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 68.73±20.76, T2= 77.03±20.93 T1= 80.87±4.41,T2= 76.45±8.32 T1= 1.38±0.42, T2= 1.30±0.53	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16
Yosry et al. (2018)	Baseline Values Volume of ascites removed() Na (mEq/) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine creatinine clearance MAP Serum creatinine Serum creatinine	T1=5.80±0.92,T2= 6.13±0.81 T1=52.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=2.68.44±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.36±0.32,T2= 1.24±0.28 T1= 68.73±2.0.76, T2= 77.03±20.93 T1= 80.87±4.41,T2= 76.45±8.32 T1= 1.38±0.42,T2= 1.30±0.53 T1= 70.96±23.49T2= 80.11±9.81	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16 58.14±19.84
Yosry et al. (2018)	Baseline Values Volume of ascites removed(I) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance MAP Serum creatinine Creatinine clearance	T1=5.80±0.92,T2= 6.13±0.81 T1=5.80±0.92,T2= 6.13±0.81 T1=1.32.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 80.87±4.41,T2= 77.03±20.93 T1= 80.87±4.41,T2= 76.45±6.32 T1= 1.38±0.42, T2= 1.30±0.53 T1= 70.96±23.49T2= 80.11±29.81 T1= 958±217.31,T2= 1169.56±309.96	1.0042530 5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16 58.14±19.84 1104.35±251.32
Yosry et al. (2018)	Baseline Values Volume of ascites removed(J) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance MAP Serum creatinine Creatinine clearance Urinary Volume	T1=5.80±0.92,T2= 6.13±0.81 T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 7.8.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 68.73±20.76, T2= 77.03±20.93 T1= 80.87±4.41,T2= 76.45±8.32 T1= 1.38±0.42, T2= 1.30±0.53 T1= 0.96±23.49T2= 80.11±29.81 T1= 958±217.31,T2= 1169.56±309.96 T1=28±13,T2= 29±14	1.00425.00 5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16 58.14±19.84 1104.35±251.32 26±15
Yosry et al. (2018)	Baseline Values Volume of ascites removed(J) Na (mEq/I) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance MAP Serum creatinine Creatinine clearance Creatinine clearance Urinary Volume U-Na So Day mortality:	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1=82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1=68.73±20.76,T2= 77.03±20.93 T1=80.87±4.41,T2= 76.45±8.32 T1=1.38±0.42,T2= 1.30±0.53 T1=70.64±23.49T2= 80.11±29.81 T1=958±217.31,T2= 1169.56±30.96 T1=28±13,T2= 29±14 T1=0; T2=2	1.00425.00 5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16 58.14±19.84 1104.35±251.32 26±15 2
Yosry et al. (2018)	Baseline Values Volume of ascites removed(J) Na (mEq/J) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented MAP Serum creatinine Creatinine clearance MAP Serum creatinine Creatinine clearance Creatinine clearance Creatinine clearance Creatinine clearance Creatinine clearance Creatinine clearance	T1=5.80±0.92,T2= 6.13±0.81 T1=52.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1=82.2±5.06,T2= 7.8.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1=68.73±20.76,T2= 7.03±20.93 T1=80.87±4.41,T2= 7.64±±8.32 T1=1.38±0.42,T2= 1.30±0.53 T1=00,6±23.49T2= 80.11±29.81 T1=958±217.31,T2= 1199.56±30.96 T1=28±13,T2= 29±14 T1=0; T2=2 2012	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16 56.14±19.84 1104.35±251.32 26±15 2 4
Yosry et al. (2018)	Baseline Values Volume of ascites removed(J) Na (mEq/l) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented d) MAP Serum creatinine Creatinine clearance MAP Serum creatinine Greatinine clearance Urinary Volume Urinary Volume Uo Day mortality: Year	T1=5.80±0.92,T2= 6.13±0.81 T1=132.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1= 82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1= 80.87±4.41,T2= 77.03±20.93 T1= 80.87±4.41,T2= 76.45±8.32 T1= 1.38±0.42, T2= 1.30±0.53 T1= 05±217.31,T2= 1199.56±30.96 T1=28±13,T2= 29±14 T1=0; T2=2 2012 RCT	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16 56.14±19.84 1104.35±251.32 26±15 2
Yosry et al. (2018)	Baseline Values Volume of ascites removed(J) Na (mEq/l) Creatine(mg/dL Urinary Na (mEq/L) Outcome on Day 6 (Presented of APP) Serum creatinine Creatinine clearance on Day 30 KAP Serum creatinine Creatinine clearance Urinary Volume Urinary Volume 30 Day mortality: Year Study design Total participants	T1=5.80±0.92,T2= 6.13±0.81 T1=52.68±3.34,T2= 132.24±3.49 T1=1.22±0.22,T2= 1.24±0.20 T1=26.84±8.68,T2= 23.28±6.23 in mean ±SD/ median(IQR) T1=82.2±5.06,T2= 78.47±4.22 T1=1.35±0.32,T2= 1.24±0.28 T1=68.73±20.76,T2= 77.03±20.93 T1=68.73±20.76,T2= 77.03±20.93 T1=68.73±20.76,T2= 71.13±0.42,T2= 1.30±0.53 T1=70.96±23.49T2= 80.11±29.81 T1=958±217.31,T2= 1169.56±30.96 T1=28±13,T2= 29±14 T1=0;T2=2 2012 RCT	5.66±0.83 130.88±3.06 1.24±0.17 27.52±11.27 83.27±4.72 1.48±0.32 61.21±23.06 80.94±4.35 1.23±0.16 58.14±19.84 1104.35±251.32 2±15 2

	Description	Saline solution (albumin placebo) Octreotide 20 mg extended release IM every month Midodrine 10mg PO 3 times a day	IV albumin 8 g/L of ascites fluid removed Saline solution 5 mL IM (octreotide placebo) every month Midodrine placebo 3 times a day		
	Population characteristics				
	Participants	12	13		
	Male (number/total)	12/12	10/13		
	Female (number/total)	0	3/13		
AGE median (IQR)		60(51-61)	55(51-65)		
	Baseline Values				
Bari et al. (2012)	Amount of ascites removed	8 (6-10.5)	6.5 (5–9.5)		
	Creatinine level. (mg/dL)	1.1 (1–1.5)	1.1 (0.9–1.5)		
	MELD score	14 (13-16)	17 (11–20)		
	Serum aldosterone level.				
	(ng/dL)	42 (12–100)	36 (18–89)		
	PRA, (ng/mL/hr)	11.8 (7.9–25.1)	19 (17.4–34.5)		
	Outcome on Day 6				
	Serum Creatinine	1.2(1.0-1.8)	0.9(0.9-1.4)		
	MELD score T	15(12-18)	14(10-16)		
	Change in PRA	↑7.1 (-22 to 67)	↓1.3(-51 to 40)		
	Change in MAP	↓2(-7 to 5)	↓5(-7 to 2)		
	Patients who developed PICD	2/8	2/11		
	10 months mortality	5/12	4/13		
	Year	2014			
	Study design	RCT			
	Total participants	50			
	Description	Midodrine was administered orally at the dosage of 12.5 mg every 8 hours for 3 days	IV albumin 8 g/L of ascites fluid removed		
	Population characteristics				
	Participants	25	25		
	Male(number/total)	17/25	21/25		
	Female(number/total)	8/25	4/25		
	Age mean +SD	55 88+5 118	58 16+3 436		
	Weight (kg)	74.28+5.77	77 92+7 314		
	Baseline Values				
	MELD score	15 326+4 34	15 01+3 84		
Llowdurat	Ascitic fluid removed(L)	6 84+ 0 718	6 96 +1 040		
al. (2014)	Serum albumin (g/dL)	2 372+ 0 4297	2 629+0 4572		
	MAR (mmHa)	79.00 ± 5.52	2.02910.4972		
	MAP (MMP)	76.99 ± 5.52	1 10 + 0.22		
	Serum creatinine (riig/dL)	0.99 ±0.19	1.10 ± 0.22		
	Plasma renin (ng/mi/n)	3.03 ± 0.33	4 ± 0.91		
	PAC (pg/mL)	166.72 ± 64.26	204.88 ± 115.9		
	Outcome				
	On day 6				
	MAP (mmHg)	71.93 ± 5.8	71.36 ± 7.81		
	Serum creatinine(mg/dL)	0.992± 0.1977	1.104± 0.2169		
	PRA (ng/ml/h)	4.2 ± 0.76	4.11 ± 0.74		
	PAC (pg/mL)	298.64 ± 130.8	177.08 ± 100.5		
	Adverse outcomes				
	HRS(number/total)	9/25	0		
	Death rate(number/total)	7/25	0		
	Year	2016			
	Study design	RCT			
	Total participants	600			
	Description	Midodrine and rifaximin were prescribed as oral midodrine 5 mg every 8 h and rifaximin 550 mg every 12 h, along with the diuretics	Combination of alternative diuretics such as torsemide 20– 40 mg/day and amiloride 5–10 mg/day, as long as creatinine clearance was greater than or equal to 50 ml/min.		
	Population characteristics				
	Participants	400	200		
	Male(number/total)	303/400	150/200		
	Female(number/total)	97/400	50/200		
	Age mean +SD	51.5 ± 6.1	52 ± 5		
	Age mean 100		52 ± 5		
	Baseline Values				

	Weight(kg)	84.4 + 8	80.3 + 4.7
	Creating (mg/dl)	15,02	14.02
		1.5 ± 0.2	1.4 1 0.2
	Creatinine clearance(ml/min)	69.4 ± 11	71.3 ± 14.2
	U-Na(meq/24 h)	16.5 ± 3.6	17.2 ± 2.2
	Urine output (ml/24 h)	528.6 ± 101	580 ± 130
Hanafy et	PRA(ng/ml/h)	4.5 ± 1.2	3.9 ± 0.9
al. (2016)	PAC (ng/dL)	21.6 ± 5.6	19 ± 3.7
	MELD	22.7 ± 2	22.1 ± 2.4
	Outcome		
	2 nd Follow up week		
	MAP (mmHg)	84.3 + 5.6	80.6 + 5
	Creatinine/mg/dl	14+016	14+02
	Creatinine character (ml/min)	66.1 + 10.2	67.4 + 40.4
	LI No (mon/24 h)	00.1 ± 10.5	10.5 + 2.4
	U-INa (meq/24 m)	25.5 ± 4.5	19.5 ± 2.1
	Unne output (mi/24 h)	927 ± 119	787 ± 99
	PRA(ng/ml/h)	3.5 ± 0.7	4.9 ± 1
	PAC (ng/dL)	19.5 ± 4.1	20.3 ± 3.4
	MELD	22.2 ± 1.8	22.7 ± 1.5
	Response Rate		
	Complete Responders(number/total)	320/400	40/200
	Partial Responders(number/total)	56/400	100/200
	Non- Responders(number/total)	24/400	18/200
	Survival (Months)	19.6 ± 3.2	11.6 ± 2.2
	Death Rate(number/total)	12/400	40/200
	Year	2005	
	Study design		
	Total participants	25	
	Description	Octreotide 300 µg, b.i.d. combined with midodrine hydrochloride 7.5 mg, t.i.d.	subcutaneous octreotide alone
	Population characteristics		
	Population characteristics Participants	13	12
	Population characteristics Participants Male(number/total)	13 7/13	12 6/12
	Population characteristics Participants Male(number/total) Female(number/total)	13 7/13 6/13	12 6/12 6/12
	Population characteristics Participants Male(number/total) Female(number/total) Age mean	13 7/13 6/13 54(40-77)	12 6/12 6/12 56(43-75)
	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values	13 7/13 6/13 54(40-77)	12 6/12 6/12 56(43-75)
	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg)	13 7/13 6/13 54(40-77) 79.4 (74-82.6)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2)
Kalamhokis	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 6.2 (5.8-6.9)
Kalambokis et al.	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 6.2 (5.8-6.9) 68 (65-84)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1)	12 6/12 6/12 56(3-75) 79.9(70.4-86.2) 6.2 (5.8-6.9) 68 (65-84) 0.8 (0.7-1)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) U-Na(meg/24 h) Urine output (ml/24 h)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 6.2 (5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.86 (0.6-1.05)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h) Urine output (ml/24 h) PRA (µU/ml)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8)	12 6/12 6/12 56/43-75) 79.9(70.4-86.2) 62.(5.8-6.9) 68.(65-84) 0.8(0.7.1) 21.(14-48.6)] 0.86(0.6-1.05) 66.(22.148.8)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8) 82.5 (40.3-144)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.8 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8) 82.5 (40.3-144)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 62.(5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.88 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10 MAP (mmHg)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8) 82.5 (40.3-144) 80.6 (70.7-83.3)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.86 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (I /min)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (68.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8) 82.5 (40.3-144) 80.6 (70.7-83.3) 6 8 (6 4-7 2)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.8 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6.5 (25.4 2)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Age mean MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (68.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8) 82.5 (40.3-144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-11)	12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 64 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.8 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (5.2-6.2) 0.8 (0.7-1)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) U-Na(meq/24 h) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) Serum creatinine(mg/dL)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8) 82.5 (40.3-144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11.45 0)	12 6/12 6/12 6/12 6/12 6/12 6/14 6/15 6/16 79.9(70.4-86.2) 62 (5.8-6.9) 63 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.8 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (5.2-6.2) 0.8 (0.7-1.1) 28.7 (16.5(7.3)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) Serum creatinine(mg/dL) Uitcome en day 10 MAP (mmHg) Cardiac Output (L/min) Serum creatinine(mg/dL) Uitcome en day 10 MaP (mmHg) Cardiac Output (L/min) Serum creatinine(mg/dL) Uitcom en day 10	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 - 183.8) 82.5 (40.3-144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9)	12 6/12 6/12 6/12 56(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 63 (65-84) 0.8 (0.7-1) 21 (14-46.6)] 0.8 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (52-6.2) 0.8 (0.7-1.1) 28.7 (18.5-47.3)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) Serum creatinine(mg/dL) Urine output (ml/min) BPA (µL/m ²)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 - 183.8) 82.5 (40.3-144) 0.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 0.6 (8.4 (4.2 - 10.2)	12 6/12 6/12 56(3-75) 79.9(70.4-86.2) 62 (5.8-6.9) 63 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.86 (0.6-1.05) 66 (22.148.8) 3.9.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (5.2-6.2) 0.8 (0.7-1.1) 23.7 (18.5-47.3) 1.11 (0.76-1.59)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/ml) PRA (µU/ml) Cardiac Output (L/min) Serum creatinine(mg/dL) Urona (mathag) Cardiac Output (L/min) Serum creatinine(mg/dL) Urona (mathag) Urona (mathag) Cardiac Output (ml/min) PRA (µU/ml) PRA (µU/ml)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 - 183.8) 82.5 (40.3-144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 26.8 (17.3 - 110.9)	12 6/12 6/12 5(4)-75) 79.9(70.4-86.2) 62 62 (5.8-6.9) 63 (65-84) 0.8 (0.7-1) 21 (14-48.6)] 0.86 (0.6-1.05) 66 (22.148.8) 32.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (5.2-6.2) 0.8 (0.7-1.1) 22.7 (18.5-47.3) 1.11 (0.76-1.59) 31.8 (6.7-64.8)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (nmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) Gardiac Output (L/min) Gardiac Output (L/min) PRA (µU/ml) Cardiac Output (L/min) Promute (ml/min)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 - 183.8) 82.5 (40.3-144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 26.8 (17.3 - 110.9) 19.9 (17.6 - 100.6)	12 6/12 6/12 5(4)-75) 79.9(70.4-86.2) 62 (5.8-6.9) 63 (65-84) 08 (0.7-1) 21 (14-48.6) 0.86 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (17.5-94.3) 6 (5.2-6.2) 0.8 (0.7-1.1) 28.7 (18.5-47.3) 1.11 (0.76-1.59) 31.8 (6.7-64.8) 1.11 (0.74.7.7)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (nmHg) Cardiac Output (L/min) Weight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Cardiac Output (L/min) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/ml) Pard (ng/dL) Quicome on day 10 Gardiac Output (L/min) Serum creatinine(mg/dL) Urine output (ml/min) PAC (ng/dL) Quicine output (ml/min) PAR (µU/ml) PRA (µU/ml) PAC (ng/dL) PAC (ng/dL)	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 - 183.8) 82.5 (40.3-144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 26.8 (17.3 - 110.9) 19.9 (17.6-100.6) 2007	12 6/12 6/12 5(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6) 0.86 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (52-62) 0.8 (0.7-1.1) 28.7 (18.5-87.3) 1.11 (0.76-1.59) 31.8 (6.7-64.8) 1.11 (3.1-47.7)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/ml) PAC (ng/dL) Cardiac Output (L/min) Serum creatinine(mg/dL) Urine output (ml/24 h) PAC (ng/dL) Cardiac Output (L/min) Serum creatinine(mg/dL) Urine output (ml/min) PAC (ng/dL) Verna (metg/24 h) Urine output (ml/min) PAA (µU/ml) PAA (µU/ml) PAC (ng/dL) Vera Vera	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 -183.8) 82.5 (40.3 -144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 2.68 (17.3 -110.9) 19.9 (17.6 -100.6) 19.9 (17.6 -100.6) 2007 RC	12 6/12 6/12 5(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 63 (65-84) 0.8 (0.7-1) 21 (14-48.6) 0.86 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (52-62) 0.8 (0.7-1.1) 22.7 (18.5-47.3) 1.11 (0.76-1.59) 31.8 (6.7-64.8) 1.11 (3.1-47.7)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(Kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PRA (µU/mi) PAC (ng/dL) Cardiac Output (L/min) Baseline Values Outone on day 10 Cardiac Output (L/min) Cardiac Output (L/min) PAC (ng/dL) Urine output (ml/min) PAR (µU/mi) PAR (µU/mi) PAR (µU/mi) Veine output (ml/min) Veine output (ml/min) Veine output (ml/min) PAG (ng/dL) Year Study design	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.97 (0.79-1.11) 109.9 (81.3 - 183.8) 82.5 (40.3-144) 82.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 2.64 (17.3 - 110.9) 19.9 (17.6 - 100.6) 2007 RCT 20	12 6/12 6/12 5(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 68 (65-84) 0.8 (0.7-1) 21 (14-48.6) 0.8 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (52-62) 0.8 (0.7-1.1) 28.7 (18.5-47.3) 1.11 (0.76-1.59) 31.8 (6.7-64.8) 1.1.1 (3.1-47.7)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) Serum creatinine(mg/dL) Uhrom output (ml/24 h) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) PAC (ng/dL) Une output (ml/min) PAC (ng/dL) Vara Vard (md) PAC (ng/dL) Vara Study design Total participants Description	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (58-62) 70.5 (68.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.9 (0.7-1) 109.9 (81.3 - 183.8) 82.5 (40.3 - 144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 26.4 (17.3 - 110.9) 19.9 (17.6-100.6) 2007 RCT 20 Oral midodrine 10 mg, ti.d.	12 6/12 6/12 6/12 6/12 5(43-75) 79.9(70.4-86.2) 62 (5.8-6.9) 62 (65-84) 08 (0.7-1) 21 (14-48.6)] 08 (0.6-1.05) 66 (22-148.8) 39.4 (15.3-91.9) 82.1 (77.5-94.3) 6 (5.2-62) 0.8 (0.7-1.1) 28.7 (18.5-47.3) 1.11 (0.76-1.59) 31.8 (6.7-64.8) 1.11 (3.1-47.7)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) Urine output (ml/24 h) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) PAC (ng/dL) Urine output (ml/min) PAC (ng/dL) Varia Varia Varia Varia Study design Total participants Description Population characteristics	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.9 (0.7-1) 109.9 (81.3 - 183.8) 82.5 (40.3 - 144) 80.6 (70.7-83.3) 6.8 (6.4-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 26.6 (17.3 - 110.9) 19.9 (17.6-100.6) 2007 RCT 20 Oral midodrine 10 mg, t.i.d. for 7 days	12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 6/12 12 6/2 10 6/2 6/2 6/2 6/2 6/2 6/2 7.1
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Veight(kg) Serum creatinine(mg/dL) Urha (meq/24 h) Valcong of a day 10 PAC (ng/dL) Outcome on day 10 Gardiac Output (L/min) PAC (ng/dL) Outcome on day 10 Varian Coutput (L/min) PAC (ng/dL) PAR (µU/ml) PAR (µU/	13 7/13 6/13 54(40-77) 79.4 (74-82.6) 6 (58-62) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.9 (0.7-1).1) 109.9 (81.3 - 183.8) 82.5 (40.3 - 144) 80.6 (70.7-83.3) 6.8 (64-7.2) 0.9 (0.7-1.1) 17.1 (11-45.9) 0.83 (0.76-0.93) 26.8 (17.3 - 110.9) 19.9 (17.6-100.6) 2007 RCT 20 Oral midodrine 10 mg, t.i.d. for 7 days 12	12 612 612 6142 6142 6142 6143 6142 6142 6142 6142 6142 6142 6142 6143 79.9(70.4-86.2) 6165-84) 6165-84) 6165-84) 6165-84) 6162-148.6) 6162-148.8) 304 (15.3-91.9) 81(177.5-94.3) 6152-62) 616(7-11) 82(177.5-94.3) 6152-62) 111(0.76-1.59) 318 (6.7-64.8) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-147.7) 11.1 (3.1-147.7) 11.1 (3.1-147.7) 11.1 (3.1-147.7)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Velyht(kg) Serum creatinine(mg/dL) Urha(meq/24 h) Valcong output (U/min) PAC (ng/dL) Outcome on day 10 MAP (mmHg) Cardiac Output (L/min) PAC (ng/dL) Outcome on day 10 Valme (a/24 h) Cardiac Output (U/min) PAC (ng/dL) PAR (µU/ml) PAR (13 7/13 6/13 5/4(0-77) 79.4 (74-82.6) 6 (5.8-6.2) 70.9 (0.7-10) 20 (10.5 - 40.2) 0.90 (0.7-11) 10.90 (81.3 - 183.8) 82.5 (40.3 - 144) 80.6 (70.7 - 83.3) 6.8 (6.4 - 7.2) 0.90 (0.7 - 1.1) 10.91 (0.7 - 1.1) 82.5 (40.3 - 144) 82.5 (40.3 - 144) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 10.91 (0.7 - 1.1) 11.45 (0.7 - 0.93) 12.91 (0.7 - 0.91) 12.91 (0.7 - 0.91) 12.91 (0.7 - 0.91) 12.91 (0.7 - 0.91) 12.91 (0.7 - 0.91)	12 6/12 6/12 5(43-75) 79.9(70.4-86.2) 612 62 (5.8-6.9) 63 (65-84) 0.8 (0.7-1) 21 (14-48.6) 0.8 (0.6-1.05) 64 (22-148.8) 39.4 (15.3-91.9) 82 (177.5-94.3) 6 (52-62) 0.8 (0.7-1.1) 22.7 (18.5-87.3) 1.11 (0.76-1.59) 31.8 (6.7-64.8) 1.11 (3.1-47.7) 1.11 (3.1-47.7) 1.11 (3.1-47.7) 1.11 (3.1-47.7) 1.11 (3.1-47.7) 1.11 (3.1-47.7) 1.11 (3.1-47.7) 1.11 (3.1-47.7) 1.11 (3.1-47.7)
Kalambokis et al. (2005)	Population characteristics Participants Male(number/total) Female(number/total) Age mean Baseline Values MAP (mmHg) Cardiac Output (L/min) Velyht(kg) Serum creatinine(mg/dL) Urha(meq/24 h) Valcong output (U/min) PAC (ng/dL) Outcome on day 10 Gardiac Output (L/min) Valcong output (U/min) PAC (ng/dL) Varime coutput (M/min) PAC (ng/dL) Parime coutput (M/min) PAC (ng/dL) Parime coutput (M/min) PAC (ng/dL) Parime coutput (M/min) PAC (ng/dL)	13 1/13 6/13 5/4(0-77) 79.4 (74-82.6) 6 (58-6.2) 70.5 (69.5-78) 0.9 (0.7-1) 22 (16.5-40.2) 0.90 (0.7) 109.9 (81.3 - 183.8) 82.5 (40.3 - 144) 80.6 (70.7-83.3) 6.8 (64-7.2) 0.90 (0.7-1.1) 17.1 (11-45.9) 0.93 (0.76-0.93) 2.63 (17.3 - 110.9) 19.9 (17.6 - 100.6) 19.9 (17.6 - 100.6) 19.9 (17.6 - 100.6) 10.9 (7 days) 12 6/12 6/12	12 6/12 6/12 6/12 5(43-75) 79,9(70.4-86.2) 612 62 (5.8-6.9) 63 (65-84) 0.8 (0.7-1) 21 (14-48.6) 0.8 (0.6-1.05) 64 (22-148.8) 30.4 (15.3-91.9) 82 (17.5-94.3) 6 (52-62) 10 (30, 7-1.1) 22.7 (75-54.3) 11.1 (3.6-1.59) 31.8 (6.7-64.8) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7) 11.1 (3.1-47.7)

	Baseline Values		
	MAP	84.4 ± 11.9	82.8 ± 10.5
Kalambokis et al.	CICre	84.4 ± 14.3	89.5 ± 12.9
(2007)	Una	29.6 ± 14.8	23.7 ±15
	UV(ml/minute)	0.98± 0.26	0.93 ± 0.41
	PRA	8.55 ± 4.24	8.2 ± 3.98
	PA	398 ± 101	340 ± 83
	Outcome on 7 days		
	MAP	90.2 ± 10	84.1 ± 9.8
	CO.	61+13	69+12
	CICre	101 + 12.6	035+11
	Una	48.8 + 15.9	28.2 + 16.7
		40.0 ± 13.9	20.2 ± 10.7
		1.15±0.34	2.04 + 0.05
	PRA(ng/mL/n)	5.57 ± 3.14	7.81±3.25
	PA (pg/mL)	223 ± 96	318 ± 83
	Year	2011	
	Study design	RCT	
	Total participants	34	
	Description	7.5 mg oral midodrine three times daily for 3 days.	50 mg subcutaneous octreotide three times daily for 3 days
	Population characteristics		
	Participants	17	17
	Male(number/total)	12/17	14/17
Minakari et	Female(number/total)	5/17	3/17
uii (2011)	Age mean	59.47 ± 14.08	49.59 ± 18.03
	Baseline Values		
	PRA (ng/ml/h)	30.99 ± 10.93	28.32 ±8.65
	MAP (mmHg)	73.84 ± 10	78.43 ±8.13
	Weight (Kg)	67.47 ± 11.16	76.58 ± 17.73
	Outcome on day 4, (mean ± S	D)	
	PRA	12.94 ± 7.62	20.64 ± 8.23
	MAP	81.57 ± 11.25	85.19 ± 7.9
	Year	2010	
	Study design	RCT	
	Total participants	15	
	Description	Midodrine 15 mg PO and furosemide 40 mg IV	Placebo (orally given 30 min before) and furosemide 40 mg intravenously
	Population characteristics		
	Participants		
	Male(number/total)	8/15	
	Female(number/total)	7/15	
Misra et al.	Age mean	(52.7±7.6)	
(2010)	MELD	(12.1±2.5)	
	Weight	80.7± 14	
	Systolic blood pressure (mmHg)	114± 15.4	
	Serum albumin (gm/dL)	3± 0.5	
	Serum creatinine (mg/dL)	1.06 ±0.2	
	Outcome 0-6 hour		
	Total urine volume (mL)	1770± 262	1962± 170
	Total urinary sodium (mMol)	109± 42	126± 69
	Year	2016	
	Study design	RCT	
	Total participants	25	
	Description	Oral midodrine 7.5 mg 8 hourly	SMT - restriction of sodium - treatment with diuretics i.e (furosemide 40-160mg/day) and a distal acting diuretic (spironolactone 100-400mg/day) was given with dose escalation by one step at a time permitted for a >10-pound weight gainand -repeated large volume paracentesis (LVP)
	Population characteristics		
	Participants	13	12
	Male(number/total)	8/13	11/12
	Female(number/total)	5/13	1/12
	Weight:	70.0±10.1	66.4±11.4
	Baseline Values		
	MELD score	14.9±2.3	16.1±2.5

	MAP	80.5±4.6	84.5±7.1
	CO	5.85±0.20	5.88±0.33
	Una	70.2±32.2	58.8±22.4
	PRA	11.7±2.5	13.8±2.6
	PA	1530.7±268.9	1555.8±238.4
	Serum Creatinine	0.89±0.28	0.78±0.21
	Urine Output(L/day)	1.08±0.27	1.26±0.35
	Outcome on 1 month		
Rai et al. 2016)	MELD Score	14 3+1 48	18 0+2 69
,	MAR	T-99 1+6 0	92 1+5 5
	WAF	1=00.1±0.0	52.113.3
	0	5.81±0.19	5.86±0.29
	U-Na	118.6±33.8	75.8±20.5
	PRA	8.5±1.4	13.8±2.8
	PA	1147.6±316.7	1527.5±300.2
	Serum Creatinine	0.84±0.19	0.87±0.34
	Urine Output(L/day)	1.44±0.27	1.20±0.23
	At 3 months		
	MELD Sore	14.6±1.06	15.8±2.91
	MAP	90.3±3.6	83.7±7.6
	со	5.73±0.22	5.78±0.33
	U-Na	111.2±26.9	79.9±10.5
	Serum Creatinine	0.84±0.19	0.80±0.10
	Urine Output	1.45+0.24	1 12+0 29
	Mortality rate and Morbidity		
	rate		
	Death :(number/total)	1/13	1/12
	Encephalopathy(number/total)	0	1/12
	Renal failure(number/total)	0	4/12
	SBP(number/total)	0	2/12
	Sensis/number/total)	1 /13	2/12
	Voor	2008	2772
	Study docion	PCT	
	Study design	RC1	
	l otal participants	40	
	Description	Midodrine 5–10 mg three times a day	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 \pm 12.1 g)
	Description Population characteristics	Midodrine 5–10 mg three times a day	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 \pm 12.1 g)
	Description Population characteristics Participants	Midodrine 5–10 mg three times a day 20	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g)
	Description Population characteristics Participants Male(number/lotal)	Midodrine 5–10 mg three times a day 20 18/20	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20
	Description Population characteristics Participants Male(number/total) Female(number/total)	Midodrine 5–10 mg three times a day 20 18/20 2/20	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20
	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean +SD	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 + 11.26	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45 05 + 14 16
	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Parenino Motivor	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16
	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16
	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63
	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.80 ± 29.75
	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.80 ± 29.75 43.18 ± 10.73
Singh et al.	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA PA	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.80 ± 29.75 43.18 ± 10.73 1,890.00±590.18
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA PA SerumCreatinine	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17	Abbumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.80 ± 29.75 43.18 ± 10.73 1.890.00±590.18 0.85±0.17
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PA PA SerumCreatinine UrineOutput(ml/day)	Nidodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1.640.00±539.40 0.79±0.17 1.495.00 ± 337.91	Abbumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 8.80 ± 29.75 18.80 ± 29.75 43.18 ± 10.73 1.890.00±590.18 0.85±0.17 1,540.00 ± 440.57
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA PA SerumCreatinine UrineOutput(ml/day) Outcome Day 6	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91	Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.5.05 ± 14.16 8.8.0 ± 29.75 4.3.18 ± 10.73 1.890.00±590.18 0.85±0.17 1.540.00 ± 440.57
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA PRA SerumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91	Abbumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.505 ± 14.16 8.80 ± 29.75 4.3.18 ± 10.73 1.890.00±590.18 0.85±0.17 1.540.00 ± 440.57
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA PRA SerumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP UNA	Nidodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1.495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38	Abumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.5.05 ± 14.16 8.5.05 ± 14.16 18.80 ± 29.75 4.3.18 ± 10.73 1.890.00±590.18 0.85±0.17 1.540.00 ± 440.57 87.00 ± 7.23 22.55 ± 28.65
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA PRA PA SerrumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP UNA	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21	Abbumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 20 17/20 3/20 4.5.05 ± 14.16 8.5.05 ± 14.16 8.5.05 ± 14.16 1.5.05 ± 14.16 ± 14.15 \pm 14.
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA PA SerumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP UNa PRA PA	Nidodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1.640.01±539.40 0.79±0.17 1.495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21	Abumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.80 ± 29.75 43.18 ± 10.73 1,890.00±590.18 0.85±0.17 1,540.00 ± 440.57 87.00 ± 7.23 22.55 ± 28.65 45.90 ± 8.59 1,965.00 ± 497.65
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP UNa PRA INA SerumCreatinine INA	Midodrine 5–10 mg three times a day 20 18/20 2120 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21	Abumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.5 0.5 ± 14.16 8.6 ± 14.16 <
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP UNa FRA UNA UNA COUTONE DAY COUTON	Midodrine 5–10 mg three times a day 20 18/20 2120 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52	Abumin & g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.5.0 ± 14.16 8.5.8 ± 6.63 18.80 ± 29.75 43.18 ± 10.73 1,890.00±590.18 0.85£.17 1,540.00 ± 440.57 87.00 ± 7.23 22.55 ± 28.65 45.90 ± 8.59 1,965.00 ± 497.65 0.98 ± 0.25 1,555.00 ± 527.63
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA Serum Creatinine UrineOutput(ml/day) Outcome Day 6 MAP UNa FRA	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52	Abumin & g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.5.0 ± 14.16 8.5.0 ± 6.63 18.80 ± 29.75 4.5.0 ± 14.16 18.80 ± 29.75 4.3.18 ± 10.73 1.890.00±590.18 0.85±0.17 1.540.00 ± 440.57 87.00 ± 7.23 2.5.5 ± 28.65 45.90 ± 8.59 1.965.00 ± 497.65 0.98 ± 0.25 1.555.00 ± 527.63
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP UNa PRA UNa ERA UNA PRA PA UNA PRA PA UNA PRA PA	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52	Abumin & g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.5.0 ± 14.16 8.5.0 ± 6.63 18.60 ± 29.75 4.5.0 ± 14.16 18.80 ± 29.75 4.3.18 ± 10.73 1.890.00±590.18 0.85£0.17 1.540.00 ± 440.57 87.00 ± 7.23 2.5.5 ± 28.65 45.90 ± 8.59 1.965.00 ± 497.65 0.98 ± 0.25 1.555.00 ± 527.63 2.20
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UrineOutput(ml/day) Outcome Day 6 MAP UNa ERA ENA ENA ENA ENA ENA ENA ENA ENA ENA EN	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52 1,640.00 ± 388.52	Abumin & g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 4.5.0 ± 14.16 8.5.0 ± 6.63 18.60 ± 29.75 4.5.0 ± 10.73 1.89.0 0.0±590.18 0.85.0.17 1.540.00 ± 440.57 87.00 ± 7.23 2.5.5 ± 28.65 1.5.90 ± 62.7.63 1.965.00 ± 527.63 1.555.00 ± 527.63 2.20 0
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) Gaseline Values AGE mean ±SD Baseline Values MAP UNa PRA SerumCreatinine UnineOutput(ml/day) Outcome Day 6 MAP UNa PRA UNa Serum Creatinine UNa PRA IDNA PRA IDNA PRA IDNA PRA IDNA IDNA IDNA IDNA IDNA IDNA IDNA IDN	Midodrine 5–10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52 1,640.00 ± 388.52 0 1/20	Abumin & g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 12.1 g) 20 17/20 3/20 4.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 14.16 8.5 0.5 ± 52.63 1.5 0.5 ± 52.7.63 1.5 0.5 ± 52.7.63 2.20 0
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UNa PRA Outcome Day 6 MAP UNa PRA Outcome Day 6 UNa PRA PION Outcome Day 6 UNa PRA PON Output (ml/day) PICD Output (ml/day) PICD(number/total) Picastparacentesis (within 3 Month of treatment)	Nidodrine 5-10 mg three 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 48.45 ± 11.26 1640.00±539.40 0.79±0.17 1.495.00 ± 337.91 25.00 ± 23.38 41.39 ± 10.21 1.700.00 ± 493.11 0.86 ± 0.21 1.640.00 ± 388.52 1.640.00 ± 388.52 1.20	Abumin & g/L of ascitic fluid was removed (mean 48.4 ±) 12.1 g) 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.40 ± 29.75 43.18 ± 10.73 1.890.00±590.18 0.85±0.17 1.540.00 ± 440.57 87.00 ± 7.23 22.55 ± 28.65 1.995.00 ± 497.65 1.955.00 ± 527.63 1.555.00 ± 527.63 2/20 2/20
Singh et al. 2008)	Description Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UNa PRA Outcome Day 6 MAP UNa PRA Outcome Day 6 UNa PRA Serum Creatinine UNa Outcome Day 6 UNa PRA Serum Creatinine Unicoutput (mi/day) PICD(number/total) PICD(number/total) Response rate Repeat paracentesis (within a) Number/total)	Midodrine 5-10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52 1,20	Abumin & g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.80 ± 29.75 43.18 ± 10.73 1.890.00±590.18 0.85±0.17 1.540.00 ± 440.57 87.00 ± 7.23 22.55 ± 28.65 1.965.00 ± 497.65 0.96 ± 0.25 1.555.00 ± 527.63 1.555.00 ± 527.63 220
Singh et al. 2008)	Perceription Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UNa PRA Outcome Day 6 MAP Una PRA Outcome Day 6 UNa PRA Serum Creatinine UNa PRA Outcome Day 6 NaP PINA PRA Serum Creatinine UNa PRA Serum Creatinine UNa PRA Serum Creatinine Unine Output (mi/day) PICD(number/total) Dicath(number/total) PRA Response rate Repeat paracentesis (within a) normber/total) Year	Nidodrine 5-10 mg three times a day 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52 1,20	Abumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12 20 17/20 3/20 45.05 ± 14.16 85.85 ± 6.63 18.80 ± 29.75 43.08 ± 10.73 1.890.00±590.18 0.85±0.17 1.540.00 ± 440.57 22.55 ± 28.65 1.965.00 ± 497.65 1.965.00 ± 497.65 1.955.00 ± 527.63 1.555.00 ± 527.63 2/20
Singh et al. 2008)	Description Population characteristics Participants Hale(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UNa Outcome Day 6 MAP UNa PRA Outcome Day 6 IVIneOutput(ml/day) PRA Serum Creatinine UNa IQUotome Day 6 IQUO PRA Serum Creatinine UNa Serum Creatinine IQUO PRA Serum Creatinine IQUO PRA Serum Creatinine IQUO	Nidodrine 5-10 mg three 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.44 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52 1,20	Abumin & g/L of ascilic fluid was removed (mean 48.4 ±) 12 20 17/20 3/20 45.05 ± 14.16 8.65 ± 6.63 18.40 ± 29.75 43.18 ± 10.73 18.90.00±590.18 0.85±0.17 1.540.00 ± 440.57 2.55 ± 28.65 1.540.00 ± 440.57 2.655 ± 28.65 1.965.00 ± 497.65 0.98 ± 0.25 1.555.00 ± 527.63 1.555.00 ± 527.63 2.20
Singh et al. 2008)	Pescription Population characteristics Participants Male(number/total) Female(number/total) AGE mean ±SD Baseline Values MAP U Na PRA SerumCreatinine UtineOutput(ml/day) Outcome Day 6 MAP Una Una Outcome Day 6 MAP Una Outcome Day 6 MAP Outcome Day 6 PRA Serum Creatinine UNa PRA Serum Creatinine Output (ml/day) PICD(number/total) Patosteritorial Response rate Response rate Ropeat paracentesis (within 3) number/total) Year Study design	Nidodrine 5-10 mg three 20 18/20 2/20 48.15 ± 11.26 86.10 ± 6.90 9.60±12.42 44.45 ± 8.44 1,640.00±539.40 0.79±0.17 1,495.00 ± 337.91 87.20 ± 7.36 25.00 ± 23.38 41.39 ± 10.21 1,700.00 ± 493.11 0.86 ± 0.21 1,640.00 ± 388.52 1,640.00 ± 388.52 1,20 2012 RCT 40	Abumin 8 g/L of ascilic fluid was removed (mean 48.4 ± 12.1 g) 20 17/20 3/20 45.05 ± 14.16 8.65 ± 6.63 18.80 ± 29.75 43.18 ± 10.73 1,890.00±590.18 0.85±0.17 1,540.00 ± 440.57 22.55 ± 28.65 45.90 ± 8.59 1,965.00 ± 497.65 0.98 ± 0.25 1,555.00 ± 527.63 2/20 2/20

	Description	randomized to midodrine were given oral midodrine 7.5 mg 8 hourly	(furosemide 40-160mg/day) and a distal acting diuretic (spironolactone 100-400mg/day) was given with dose escalation by one step at a time permitted for a >10-pound weight gainand -repeated large volume paracentesis (LVP)		
	Population characteristics				
	Participants	20	20		
	Male(number/total)	17/20	20/20		
	Female(number/total)	3/20	0		
	AGE mean ±SD	45.6 ± 10.049	47.6 ± 11.033		
	Baseline Values				
	Recurrent	14/20	14/20		
	ascites(number/total)				
	Refractory ascites(number/total)	6/20	6/20		
	MELD score	12.9 ± 3.13	14.85 ± 4.68		
	Weight (kg)	68.45 ± 18.70	64.43 ± 12.15		
	Mean arterial pressure (mmHg)	85.6 ± 10.7	83.59 ± 11.44		
	со	5.68± 1.66	5.81± 1.82		
	Serum Sodium	134.6± 10.57	134.15± 5.5		
	Una	73.14± 35.63	70.47± 30.24		
	PRA	13.73± 4.41	13.12± 3.88		
	PA	1601.5± 789.7	1545.3± 630.9		
	Serum Creatinine	0.85± 0.272	1.03± 0.310		
	Serum Creatinine	0.85± 0.272	1.03± 0.310		
	Urine Output	1235± 665.12	1381.2± 636.8		
Singh et al.	Outcome on 1 month				
(2012)	Weight:	67.15± 19.78	65.5± 10.79		
	MELD Score	13.9± 4.1	16.1± 5.6		
	MAP	92.88± 7.91	83.01± 8.50		
	Una	93.21± 32.19	68.75± 18.93		
	PRA	9.66± 2.51	14.75± 3.48		
	PA	921.5± 547.8	1440.59± 497.3		
	Serum Creatinine	0.84± 0.205	1.01± 0.227		
	Urine Output(ml/day)	1830± 564.84	1496.8± 549.6		
	Response Rate				
	At 1 month				
	No of Patients	18	17		
	Complete(number/total)	2/18	0		
	Partial				
	None(number/total)	1/18	3/17		
	At 3 months				
	No of Patients	16	16		
	Complete(number/total)	5/16	1/16		
	Partial(number/total)	10/16	7/16		
	None(number/total)	1/16	8/16		
	At 6 months				
	No of Patients	12	5		
	Complete(number/total)	5/12	1/5		
	Partial(number/total)	4/12	4/5		
	None(number/total)	0	0		
	Mortality				
	1-month(number/total)	3/20	4/20		
	3 months(number/total)	7/20	11/20		
	6 months(number/total)	8/20	15/20		
	Year	2013			
	Study design	RCT			
	Total participants	30			
	Description	Oral midodrine 7.5 mg 8 hourly	SMT - restriction of sodi-um - treatment with diuretics i.e (furosemide 40-160mg/day) and a distal acting diuretic (spironolactone 100-400mg/day) was given with dose escalation by one step at a time permitted for a >10-pound weight gainand -repeated large volume paracentesis (LVP)		
	Population characteristics				
	Participants	15	15		
	Male(number/total)	14/15	15/15		
	Female(number/total)	1/15	0		
	Baseline Values				

	Recurrent ascites(number/total)	6/15	6/15
	Refractory ascites(number/total)	9/15	9/15
	Weight	67.06 ± 12.82	73.86 ± 7.94
	MELD Score	13.56 ± 5.71	13.92 ± 4.18
	MAP	85.3 ±8.72	92.6 ±6.06
	со	6.67 ±1.21	6.70± 1.36
Singh et al.	Una	42.2 ±12.6	35.6 ±14.3
(2013)	Serum Creatinine	1.03 ±0.30	1.11 ±0.20
	Urine Output(ml/day)	995.3±226.7	947.3±250.6
	PRA	12.0 ±3.00	13.6± 2.75
	PA	1512.0 ±444.1	1528.0± 497.1
	Outcome on 1 months		
	MELD Score	12.4 ±3.67	13.5 ±3.99
	MAP	94.7±4.48	87.6±5.24
	U-Na	72.5±18.1	45.2±19.6
	Serum Creatinine	1.01 ±0.25	1.13± 0.22
	Urine Output	1267.8 ±333.1	1107.8± 316.3
	PRA	9.22 ±2.74	13.8 ±2.86
	PA	820.7 ±223.9	1410.8± 332.2
	1 month mortality(number/total)	1/15	1/15
	Response Rate:		
	1 months		
	Total patients	14	12
	Complete(number/total)	-	-
	Partial(number/total)	11/14	5/12
	None(number/total)	-	-
	Year	2018	
	Study design	RCT	
	Total participants	173	
	Description	Midodrine 15mg/day or 30mg/day based on MAP goal Albumin i.v. at a dose of 40g every 15 days.	Placebo of midodrine; 0.9% saline as a placebo of albumin
	Population characteristics		
	Participants	87	86
	Male(number/total)	66/87	71/86
	Female(number/total)	21/87	15/86
	Baseline Values		
	MELD score	17±6.0	16±6.2
	MAP	80±10mmHg	81±10mmHg
Solà et al.	Serum creatinine (mg/dL)	0.96±0.3	1.0±0.4
(2018)	MAP (mmHg)	80±10	81±10
	Outcome		
	At Week 4, MELD score	13±4	13±4
	At Week 12, MELD score	13±3	13±4
	At Week 24, MELD score	13±2	12±4
	Patients with adverse event(number/total)	83/87	84/86
	Renal impairment	12/83	11/84
	Hyponatremia	11/83	14/84
	Hepatic encephalopathy	24/83	21/84
	Sepsis	12/83	13/84
	Gastrointestinal bleeding	8/83	4/84
	Mortality at 2 month	38/87	31/86
	Mortality at 6 month	68/87	51/86

TABLE 1: Narrative summary of included studies

Abbreviations: ALT= Alanite transaminase, AST= Aspartate aminotransferase, BUN= Blood urea nitrogen, C= Control group. CQ(L/min)= Cardiac output, CICree Creationie dearance, CTP score Child-Turcotte-Pugh score, EF= Ejection fraction, F= Fernale, CGRCC General Clinical Research Center, CFR(ml/min)= Giomenular fittation rate, HEV= Hapatitis & Viuse, HCC= Hepatoclidular carcinoma, HCV= Hepatitis C Viuse, HE= Hapate conceptalopathy, HR= Heart rate, HRS= Hepatorenal syndrome, INR= International normalized ratio, INR= Interquartile range, HCV= Hapatitis C Viuse, HE= Hapate conceptalopathy, HR= Heart rate, HRS= Hepatorenal syndrome, INR= International normalized ratio, INR= Interquartile range, HCV= Hapatitis C Viuse, HE= Hapate conceptalopathy, HR= Heart rate, HRS= Hepatorenal syndrome, INR= International normalized ratio, INR= Interquartile range, HCV= Hapatitis C Viuse, Heart rate, HRS= Hepatorenal syndrome, INR= International normalized ratio, INR= Interquartile range, HCV= Hapatitis C Viuse, HE= Nature Statistical Perioditis, SMT= Standard medical Herray, S-NatureRQ1, J= Serum Sodium, SVR(dynesi/scn5)= Systemic vascular resistance, T= Treatment group, UGI= Upper gastrointestinal, U-Na(mEq/24 h)= Urinary sodium, UV= Urinary volume

Alsebaey et al. (2013) [14]; Appenrodt et al. (2006) [1]; Yosry et al. (2018) [4]; Bari et al. (2012) [15]; Hamdy et al. (2014) [16]; Hanafy et al. (2016) [6]; Kalambokis et al. (2005) [8]; Kalambokis et al. (2007) [17]; Minakari et al. (2011) [16]; Misra et al. (2010) [7]; Rai et al. (2016) [19]; Singh et al. (2012) [20]; Singh et al. (2016) [16]; Singh et al. (2012) [20]; Singh et al. (2016) [16]; Singh et al. (2017) [17]; Rai et al. (2016) [19]; Singh et al. (2017) [17]; Rai et al. (2016) [19]; Singh et al. (2017) [17]; Rai et al. (2016) [19]; Singh et al. (2016) [19]; Singh et al. (2017) [17]; Rai et al. (2017) [17]; Rai et al. (2016) [19]; Singh et al. (2018) [18]; Singh et al. (2017) [17]; Rai et al. (2016) [19]; Singh et al. (2017) [17]; Rai et al. (2017) [17]; Rai et al. (2017) [17]; Rai et al. (2016) [19]; Singh et al. (2017) [17]; Rai et al. (2017)

Quantitative Analysis

Fourteen studies [1,5,4,6,8,14-22] comprising a total of 1199 patients were included in our quantitative analysis.

Mean Arterial Pressure (MAP)

A total of twelve studies reported MAP outcomes, mostly around one week of treatment. The addition of midodrine to standard medical treatment (SMT) showed a mean MAP of 2.56 mmHg higher in the midodrine group (MD, 3.95 mmHg; 195% CI, 1.53–6.36; p=0.001) compared to SMT. Midodrine when compared to albumin did not reach significant differences level in terms of MAP (MD -0.40, 95% CI -2.37 to 1.57; n= 164; 12 = 0%) (Figure 3).



FIGURE 3: Forest plots comparing MAP between midodrine and Placebo/SMT, and midodrine and albumin

The square box across the horizontal lines represents the mean difference (MD) value for the individual study, the horizontal line represents 95% confidence interval (CI), and the diamond represents the pooled MD with its CI.

MAP= Mean arterial pressure, SMT= Standard medical treatment

Included studies are reference nos. [1,3,4,6,8,16-22]

MELD Score

Six studies reported MELD (Model for End-Stage Liver Disease) scores among 14 studies included. The use of midodrine showed a significant reduction in MELD score among ascitic patients compared with SMT. Comparing midodrine with SMT showed an average of 1.27 points lower MELD score in midodrine group (MD -1.27, 95% Cl -2.49 to -0.04; n= 868; 12 = 73%) (Figure 4).

	M	dodrine		Plac	ebo or S	MT		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.1.1 Midodrine vs Placel	bo or SM	т							
Hanafy AS et al 2016 (1)	22.2	1.8	400	22.7	1.5	200	32.1%	-0.50 [-0.77, -0.23]	•
Rai N et al 2016 (2)	14.3	1.48	13	18	2.69	12	19.8%	-3.70 [-5.42, -1.98]	
Singh V et al 2012	13.9	4.1	20	16.1	5.6	20	10.8%	-2.20 [-5.24, 0.84]	
Singh V et al 2013	12.4	3.67	15	13.5	3.99	15	12.4%	-1.10 [-3.84, 1.64]	
Solà E et al 2018 (3)	13	4	87	13	4	86	24.9%	0.00 [-1.19, 1.19]	
Subtotal (95% CI)			535			333	100.0%	-1.27 [-2.49, -0.04]	-
Heterogeneity: Tau ² = 1.20	0; Chi ² = 1	15.08, dt	= 4 (P	= 0.005	; P= 739	6			
Test for overall effect: Z = :	2.03 (P =	0.04)							
5.1.2 Midodrine vs Album	in								
Bari K et al 2012	15	5.0316	12	13.27	4.9833	13	100.0%	1.73 [-2.20, 5.66]	
Subtotal (95% CI)			12			13	100.0%	1.73 [-2.20, 5.66]	
Heterogeneity: Not applica	able								
Test for overall effect: Z = I	0.86 (P =	0.39)							
									-4 -2 0 2 4
Test for subgroup differen	anni Chi	- 2.04	d - 1 /	0 - 0.16	- FO	04			Midodrine Placebo or SMT
rest for subgroup unteren	ices. oni	- 2.04,	ui – i (e = 0.15	9, I. = 50.	370			

rootnotes (1) 2nd Follow up (2) at 1 month

FIGURE 4: Forest plot comparing mean MELD score between midodrine and placebo/SMT. (Only one study compared midodrine with albumin for MELD score)

The square box across the horizontal lines represents the mean difference (MD) value for the individual study, the horizontal line represents 95% confidence interval (CI), and the diamond represents the pooled MD with its CI.

MELD= Model for End-Stage Liver Disease, SMT= Standard medical treatment

Included studies are reference nos. [6,15,19-22].

Plasma Renin Activity (PRA) (ng/ml/hr)

Overall, midodrine use caused an average of 3.49 ng/ml/hr lower PRA in the treatment group than SMT/Placebo (MD -5.49, 95% CI -5.50 to -1.49; P=0.0006). At the same time, PRA activity was not different when midodrine was compared to albumin (MD -1.25, 95% CI -5.34 to 2.85; n= 90; I2 = 58%) (Figure 5).



FIGURE 5: Forest plots comparing mean PRA between midodrine and placebo/SMT, and midodrine and albumin

A square box across the horizontal lines represents the mean difference (MD) value for the individual study, the horizontal line represents 95% confidence interval (CI), and the diamond represents the pooled MD with its CI.

PRA= Plasma renin activity, SMT= Standard medical treatment

Included studies are [3,6,8,16-21].

Plasma Aldosterone Concentration (PAC) (pg/ml)

Overall, midodrine use averages 223.48 pg/ml lower PAC in the treatment group than SMT (MD -224.48, 95% CI -391.40 to -57.56; P=0.008). Comparing midodrine to albumin did not show significant differences (MD 31.79, 95% CI -275.97 to 339.55P=0.84) (Figure \diamond).



FIGURE 6: Forest plot comparing mean PAC among midodrine and other treatments in case of ascites due to cirrhosis

The square box across the horizontal lines represents the mean difference (MD) value for the individual study, the horizontal line represents 95% confidence interval (CI), and the diamond represents the pooled MD with its CI.

PAC= Plasma aldosterone concentration

Included studies are [1,3,6,8,16,17,19-21].

Short-Term Mortality

A total of eight studies reported mortality outcomes. There were no significant differences in short-term mortality (within three months, though it was reported heterogeneously across studies noted in footnotes) when midodrine use was compared to SMT/placebo or albumin (OR, 0.52; 95% CI, 0.15 to 2.01; P=0.34 and OR, 2.05; 95% CI, 0.38 to 11.04; P=0.40 respectively) (Figure 7).



(5) Within 1 month (6) Midodrine 12.5 mg every 8 h for 2 days vs Albumin, 30 days mortality

FIGURE 7: Forest plots showing mortality comparing midodrine to SMT/Placebo and albumin

The square box across the horizontal lines represents the Odds Ratio (OR) value for the individual study, the horizontal line represents 95% confidence interval (CI), and the diamond represents the pooled OR with its CI.

SMT= Standard medical treatment

Included studies are [3,4,6,15-17,19-21].

Serum Creatinine

A total of ten studies reported serum creatinine value during the study period, mostly around one week of treatment. Midodrine use was not statistically significant in lowering serum creatinine compared to SMT/placebo; however, it was nearing statistical significance (MD, -0.06; 95% CI, -0.14 to 0.05; P-0.19). On the contrary, midodrine use leads to a statistically significant reduction in serum creatinine compared to albumin (MD, -0.09; 95% CI, -0.16 to -0.02; P=0.01) (Figure *s*).

	Mi	dodrine		Place	bo or SI	AT		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.1.1 Midodrine vs Placet	to or SMT								
Hanafy AS et al 2016 (1)	1.4	0.16	400	1.4	0.2	200	27.8%	0.00 [-0.03, 0.03]	+
Kalambokis G et al 2005	0.9	0.3322	13	0.8733	0.3354	12	4.2%	0.03 [-0.24, 0.29]	
Rai Net al 2016	0.84	0.19	13	0.87	0.34	12	5.7%	-0.03 [-0.25, 0.19]	
Singh V et al 2012	0.84	0.205	20	1.01	0.227	20	11.5%	-0.17 [-0.30, -0.04]	
Singh V et al 2013	1.01	0.25	15	1.13	0.22	15	8.5%	-0.12[-0.29, 0.05]	
Subtotal (95% CI)			461			259	57.7%	-0.06 [-0.14, 0.03]	-
Heterogeneity: Tau ^a = 0.00	l; Chi# = 7.	57, df = 4	(P = 0	11); I*= -	47%				
Test for overall effect: Z = 1	.32 (P = 0	.19)							
4.1.2 Midodrine vs Album	in								
Appenrodt B et al 2008	0.9778	0.229	11	0.9983	0.191	13	8.3%	-0.02 [-0.19, 0.15]	
Bari K et al 2012	1.3465	0.6709	12	1.0825	0.4153	13	1.6%	0.26 [-0.18, 0.71]	
Hamdy H et al 2014	0.992	0.1977	25	1.104	0.2169	25	13.8%	-0.11 [-0.23, 0.00]	
Singh V et al 2008	0.86	0.21	20	0.98	0.25	20	10.6%	-0.12 [-0.26, 0.02]	
Yosry A et al 2018	1.35	0.32	25	1.48	0.32	25	7.9%	-0.13 [-0.31, 0.05]	
Subtotal (95% CI)			93			96	42.3%	-0.09 [-0.16, -0.02]	-
Heterogeneity: Tau ^a = 0.00	I; Chi# = 3.	61, df = 4	(P=0	46); I*= I	8%				
Test for overall effect: Z = 2	2.49 (P = 0	.01)							
Total (95% CI)			554			355	100.0%	-0.07 [-0.12, -0.01]	•
Heterogeneity: Tau ^a = 0.00	l: Chi# = 16	5.12. df=	9 (P =	0.09); P=	40%			_	
Test for overall effect: Z = 2	2.24 (P = 0	.02)							-U.2 -U.1 U U.1 U.2
Test for subgroup differen	ces: Chi	= 0.38. df	= 1 (P	= 0.54). P	= 0%				midodillia bigcepo ot SW1
Englandes									

(1) 2nd Follow up week

FIGURE 8: Forest plots comparing mean serum creatinine between midodrine and placebo/SMT, and midodrine and albumin

The square box across the horizontal lines represents the mean difference (MD) value for the individual study, the horizontal line represents 95% confidence interval (CI), and the diamond represents the pooled MD with its CI.

SMT= Standard medical treatment

Included studies are [1,3,4,6,8,15,16,19-21].

Paracentesis Induced Circulatory Dysfunction (PICD)

Paracentesis Induced Circulatory Dysfunction (PICD) as an outcome was reported in four RCTs. Midodrine use did not show significant difference in PICD outcome compared to SMT (OR 1.45, 95% CI 0.58 to 3.57; n= 133; 12 = 0%) (Figure 9).

	Midodi	rine	Albun	nin		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Alsebaey A et al 2013	5	25	3	25	30.9%	1.83 [0.39, 8.67]			
Appenrodt B et al 2008	6	11	4	13	21.4%	2.70 [0.51, 14.37]			
Bari K et al 2012	2	8	2	11	16.3%	1.50 [0.16, 13.75]			
Singh V et al 2008	0	20	2	20	31.4%	0.18 [0.01, 4.01]	-		
Total (95% CI)		64		69	100.0%	1.45 [0.58, 3.57]		-	
Total events	13		11						
Heterogeneity: Chi# = 2.3	6, df = 3 (P = 0.5	0); I ^e = 09	\$6			-		100
Test for overall effect Z =	0.80 (P =	0.42)					0.01	Midodrine Albumin	100

FIGURE 9: Forest plot showing PICD comparing midodrine with other treatments in case of ascites due to cirrhosis

The square box across the horizontal lines represents the Odds Ratio (OR) value for the individual study, the horizontal line represents 95% confidence interval (CI), and the diamond represents the pooled OR with its CI.

PICD= Paracentesis induced circulatory dysfunction

Included studies are [1,3,14,15].

Publication Bias

Publication bias of the included studies was assessed and presented in Funnel plots. Significant publication bias was present as suggested by an asymmetry of the plot for outcomes evaluated (Figures 10-11).



FIGURE 10: Funnel plot showing the asymmetric distribution of studies suggesting publication bias for MAP outcome

MAP= Mean arterial pressure, SMT= Standard medical treatme



FIGURE 11: Funnel plot showing the asymmetric distribution of studies suggesting publication bias for short-term mortality outcome

SMT = Standard medical treatment

Discussion

Cirrhotic ascites is usually associated with hypotension due to vasodilation mediated by low effective control astress is usually associated with hypotension due to vasionation internated of two enecutive circulatory volume. Diuretics in such cases can further worsen renal perfusion and decrease renal sodium excretion. Midodrine is an oral vasopressor that blocks vasodilation and increases blood pressure, potentially leading to improved renal perfusion and decreased ascites [20,21,23]. This possibly leads to porchain y caung ounprotect thin periadon material accelerated as the second sector (as the second sector) is a possibly tends of the mortality and morbidity benefits. In this meta-analysis, we focused on the role of middorline in combination with drugs like rifaximin, octreotide, and clonidine in cirrhotic ascites. Different studies included rifaximin, octreotide, clonidine, albumin, terlipressin, hydroxyethyl starch (HES), a combination of alternative diuretics like torsemide, amiloride, furosemide, and spironolactone, repeated large-volume paracentesis as standard medical treatment (SMT). As expected, we found significant improvement in blood pressure patients receiving midodrine compared to standard medical treatment as a potential effect of alpha-1 mediated vasoconstriction. Midodrine use was statistically significant in lowering serum creatinine compared to albumin, however, reduction in creatinine did not reach the level of significance while compared with SMT/placebo. This is likely due to the effect of midodrine, which has been found to improv renal hemodynamics, and glomerular filtration rate (GFR) and promote sodium excretion in patients with cirrhosis [5,18,20]. In our analysis, we found midodrine to decrease plasma renin and aldosterone concentration compared to standard medical treatment alone. This is significant because this explains the beneficial effect of midodrine in paracentesis-induced circulatory dysfunction and the apparent lack of difference observed between patients treated with albumin and midodrine regarding the occurrence of PICD. Midodrine was found to improve urine output and cause weight loss in multiple studies [8,17,20]. However the patients in these studies received concomitant diuretic therapy, which also leads to these changes, and the benefit cannot be solely credited to midodrine. We also found a significant reduction in MELD scores comparing patients treated with midodrine to standard medical treatment. A reduction in MELD scores is a possible prognostic factor for patients with cirrhosis and ascites. However, a previous study suggested preversible deterioration of MELD score with midodrine, octreotide, and albumin treatment for one month in refractory ascites [24]. This might be due to the co-administration of octreotide and midodrine for one month. Our analysis of MELD scores included studies in which patients received midodrine alone and for prolonged periods.

Our analysis found no difference in PICD between patients receiving albumin and midodrine while anakzing the results of four trials that reported on PICD [1,5,14,15]. PICD was defined as increased plasma renin by 50% from baseline at day six in studies [1,14]. Therapeutic paracentesis leads to depletion of intracellular volume, thereby activating the remin-angiotensin-aldosterone system and increasing renin levels. Expansion of plasma volume with albumin decreases the risks of paracentesis-induced circulatory dysfunction in various studies. However, we found no difference in PICD between patients treated with albumin and midodrine [1,16]. This finding was similar to the previous meta-analysis done by Guo et al. [9]. However, we did not find a significant difference in short-term mortality between midodrine and SMT, midodrine and albumin. Our findings are similar to the previous meta-analysis done by Guo et al., who found no improvement in mortality at one month [9]. Sola et al. reported renal impairment, hepatic encephalopathy, gastrointestinal biedding, hyponatremia, and sepsis as some of the adverse effects of midodrine and De [22].

Our meta-analysis is the most comprehensive meta-analysis to date, including a total of 14 studies, and the second meta-analysis to evaluate the effect of midodrine in cirrhotic ascites. We have compared multiple outcomes regarding the use of midodrine in cirrhotic ascites to albumin and standard medical treatment. Terlipressin and albumin are treatments for refractory ascites, but both require intravenous access and are expensive. Our findings of midodrine being non-inferior to albumin regarding the occurrence of PICD and decrement in plasma renin and aldosteror formulation making it much easier to use. are significant because midodrine is available in cheap or

Our study has several limitations. The endpoints for assessment of our outcomes were variable ranging from day four, day 10, one month to three months [8,18-21]. In some of the studies, patients received concomitant adjuvant treatment like octreotide [8,15], and rifaximin [6]. Another significant limitation was the wide aufordant treatment into Corectore [6,13], and maximum [6]. Allotters significant initiation was the work variation in the dosage and duration of midodrine ranging from three days to months, which caused heterogeneity in the reported results. Finally, there were inherent limitations in included studies like small sample size, lack of proper randomization, short duration of midodrine treatment, etc.

Conclusions

Midodrine alone leads to statistically significant improvement in various clinical parameters in patients with cirrhotic ascites compared to standard medical care. At the same time, it appears to be non-inferior to albumin. We report that the addition of midodrine to SMT for diuretic-resistant cirrhotic ascites would be beneficial. The results from our study call for further well-designed studies evaluating the combination of midodrine and albumin for optimal clinical benefits.

Appendices

entary file 1. Electronic database search details Supplem

PubMed

Hits: 44

Search: "midodrine" AND "ascites" AND "cirrhosis"

Link: https://pubmed.ncbi.nlm.nih.gov/? term=%22midodrine%22+AND+%22ascites%22+AND+%22cirrhosis%22

PubMed Central

Hits: 255

Search: "midodrine" AND "ascites" AND "cirrhosis"

Link: https://www.ncbi.nlm.nih.gov/pmc/? term=%22midodrine%22+AND+%22ascites%22+AND+%22cirrhosis%22

Embase

Hits: 323

Search: ('midodrine'/exp OR 'midodrine') AND ('ascites'/exp OR 'ascites')

Link:

https://www.embase.com/#advancedSearch/resultspage/history.15/page.1/25.items/orderby.date/source.

Scopus

Hits: 242

Search: "midodrine" AND "ascites" AND "cirrhosis"

Link: https://www.scopus.com/results/results.uri? numberOfFields=0&src=s&clickedLink=&editSaveSearch=&origin=searchbasic&authorTab=&affiliationTab=&advancedTab=&scint=1&sciABS-

KEY % 28% 22 midodrine % 22 + AND + % 22 a crites % 22 + AND + % 22 cirrhosis % 22% 29 & sid = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 4 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 d75 b f & search 1 d = b 0 edf 479 bae 139 c7f 8 ea 1 d 1 d 48 d75 b f & search 1 d 48 d75 bf&originationType=b&rr

Study ID	Title	Country	Design	Start date	End date	Inclusion criteria	Exclusion criteria	Limitations
Alsebaey et al. 2013	Prevention of paracentesis- induced circulatory dysfunction: could we use other albumin alternatives?	Egypt	RCT	2013		The presence of lense asches determined by chricid examination and aldominal ultrasound, requiring frequent herapeutic paracentesis, age younger than 70 years and older than 18 years, and absence of articela regulations, and absence of articela physertesion, hutking of coronary disease, hepatic encephalpapthy, sepsis, spontaneous backniris perforitors, (sefmed by polymorphorucidear cell count >250/min aucites), elevated creatine concentration theyler than 1.5 mg/sl, and gastrointerianal bleeding within 7 days before the study	Not Specified	Not Specified
Appenrodt et al. 2008	Prevention of paracentesis- induced circulatory dysfunction: midodrine vs albumin.	Germany	RCT	October 2004	May 2006	The presence of liver cirrhosis with tense ascites (>5.1), determined by abdominal ultrascund and cirrical examination, requiring therapeutic paracentesis.	Patients with a prothrombin time of <30%, platete court of <30 000L, a serum creatine concentration of >1.5 mg/d those younger ham lysers and older than 70 years, Recent onset or change in diuretic therapy, and use of albumin or pancentesis as well as gastonitestial beforeign and sepsite lagonosis of spontaneous bacterial peritonitis (defined by polymorphonuclear cell court > 250min rascles) within 7 days before the study crust.	Small sample si the dose, and duration of drug administration were fixed with adaptation by hemodynamic parameters.
Yosry et al. 2018	Oral midodrine is comparable to albumin infusion in cirrhotic patients with refractory ascites undergoing large- volume paracentesis: results of a pilot study	Egypt	RCT	July 2015	April 2018	 Cirrholic patients with refractory or recurrent ascilles. 2. Patients younget than 70 years of age and older than 18 years of age. 3. Assence of applis. 4. Profitometin concentration of more than 30% and platelet courts of more than 25 6001. 5. Serum creatinine less than 1.5 mg/d. 	 Durelics dose change within 7 days before the study. 2. Spontaneous backerial peritonisis and/or gastrointes/inal bleeding within 7 days before the study. 3. Marked respiratory distress necessitaling tagetog be performed on the same day of presentation. 4. Hepatic encephalogethy or malignamor, 5. Uncontrolled diabetes (HNA-res), a strint in/pertension, history of coronary heart disease, or cardiac failure. 6. Refusal to participate in the study 	Not specified.
	The Combination of Octreotide and							Small sample s

Bari et al. 2012	Midodrine Is Not Superior to Albumin in Preventing Recurrence of Ascites After Large-Volume Paracentesis	USA	RCT	October 2003	June 2010	Age: 18-80 years Cinhosis of any etology, refractory asciles	amount of ascillas Recent (within 1 mo) gastrointestinal hemonihage Active bacterial infection Cardiac failure Findings suggestive of organic renal disease Hepatocellular carcinoma, Baseline serum creatinine level greater hun 3.0"	the dose, and duration of drug administration were fixed with no adaptation by hemodynamic parameters.
Hamdy et al. 2014	Comparison of Midodrine and Albumin in the Prevention of Paracentesis- induced Circulatory Dysfunction in Cirrhotic Patients	Egypt	RCT	November 2010	March 2012	*1. Patients with refractory ascites, less than 70 years of age and more than 18 years of age with circhosis and tense ascites (>5 L), determined by abdominal ultrasound and clinical examination, requiring therapeutic paracentesis. *	*1. The presence of arterial hypotension or hypotension, a history of corrany heart disease, cardiac failure, respiratory disease, erraid disease, uninary intertion, photochromocytoma, thyrotoxicosia, or diabetes meilitar, 2. The presence of sepsia, spontaneous bacterial periodis, hepatic encephalopathy, and gastorintestinal bleeding within 7 days before the study, 3. Recent use of diurretica or change in diuretic therapy, b- blockers, planm expanders, or paracentesis. ⁴	Small sample size, the dose, and duration of drug administration were fixed with no adaptation by hemodynamic parameters.
Hanafy et al. 2016	Rifaximin and midodrine improve clinical outcomes in refractory ascites including renal function, weight loss, and short- term survival	Egypt	RCT	November 2011	May 2015	"1. Age 18-70 years, evidence of end-stage liver disease and acticles that is erfractory to conventional therapy at the maximum tidenteid does of aptionolactore and furosemide, rapidly recurrent accides, and systolic blood pressure (SBP) less than 100 mmHg."	"1. Non-cirrhotic causes of asoles, primary renal medical diseases, any grade of unrestoved Repatic encephalopathy until it has improved and stabilized, 2, active gastrointestinal identing, HRS, provious antibiotic prophylaxes for spontaneous bacterial peritorisis, 3 the presence of hepatocellular carcinomar or portial with thombosis, active cardiovascular disease, 4. Systemic hypertension, drugs that affect systemic and renal hemodynemics, and active alcohol consumption."	Randomization was not centralized
Kalambokis et al. 2005	The Effects of Chronic Treatment with OctreoSide versus OctreoSide plus Midodrine on Systemic Hemodynamics and Renal Hemodynamics and Function in Nonazotemic Cirrhotic Patients with Ascites	Greece	RCT	January 2003	January 2004	*1. Absence of gastrointestinal bleeding, hepatic enceptalogathy, or infection within the study, 2 absence of refractory ascilles or HRS, according to the criteria recently proposed (72). 3. no treatment with duratics or other drugs with known effects on systemic and renal hemosystemics and/or on renal function within the 5 days before the inclusion. 4. positive softum blance after all tests 5 days of restricted sodium intake (80 mGyday), 5. accentral hypertension 6. absence of heptacoeffully, artificial hypertension 6. absence of heptacoeffully areas to participate.		Not specified.
Kalambokis et al. 2007	Effects of a 7-day treatment with midodrine in non- azotemic cirrholic patients with and without ascites	Greece	RCT	2006	2008	¹¹ . Absence of gas- troinestinal bleeding, hepatic morphalograph or infection within the 1 month preceding the study or during the study, 2 absence of mas- sive or tems accites, refractory accites or HRS according to the proposed criteria 3. no treatment with durintics or other drugs with income fields on systemic and remail haemodynamics and/or renal function within the 7 days before the inclusion, 4, absence of dabbes, infinite renal function on history and physical examination, absencemal unsaysis, Absence of hepatoschular carcinoma or portal vein thrombosis."		Not Specified
Minakari et al. 2011	Comparison of the effect of midodrine versus octreotide on hemodynamic status in cirrhotic patients with ascites	Iran	RCT	January 2007	January 2009	"Age more than 15 years old Do not had Gl bleeding during last 7 days and/or had an unstable hemodynamics Do not have heatic concephalopathy there on lifection (septis, spontaneous bacterial peritonitis) within the last 30 days Do not have diablese melitace Do not have cardiovascular diseases and hypertension have no proven hepatocellular carcinoma Do not have hepatoreal syndrome Have no known allergy to dugs."	Having hepatic encephalopathy Hepatorenal syndrome, hemodynamic instability infection or gastrointestinal bleeding during the course of admission	 The study could not measure some variables such as renal blood flow, cardiac output systemic vascular resistance and urinary sodium excretion. 2. Other limitations of this study were small size of the groups and short duration of treatment
Misra et al. 2010	The effects of midodrine on the natriuretic response to furosemide in cirrhotics with ascites	USA	RCT	17 April 2002	Not mentioned * published in 2010	18 Adult cirrhotic patients with clinically detectable asciles (are 118, Child - Pugh score 17) were screemed prior to enrolment, but one subject chose not to participate further during the initial equilibration phase, hence the total number of participants were 15	Congestive heart failure Creatinine clearance <00 m/umin Unitested endocrinopathies Actively consuming alcohol, Who have a TIPS.	
Rai et al. 2016	Midodrine and tolvaptan in patients with crimbosis and refractory or recurrent ascites ca randomized pilot study	India	RCT	2016	2018	"Patients with ciritosis and refractory or recurrent ascilea with stable renal function (creatione level <1.5 mg/sL for at least 7 days)"	"Gastrointestinal bleeding, hepatorenal syndrome, grade 2 or higher hepatic encephalopathy, infection within 1 month preceding or during the study, presence of diabetes, initinaic renal or cardiovascular disease or attenial hypertension on history and physical assimilator, abcorned une analysis, abnormal chest nadograph or electrocardiogram, presence of hepatocollular caranoma or polal with thromosa, teatement with drugs with known effects on systemic and renal hemodynamics (bala-blockners were withdrawn and low does diseles were continued as bibertach, provided the serum creativine as kibertach, provided the serum creativine as < 1.5 mg(L) within 7 days	-The small sample size of this pilot thil raises the potential for Type 2 error and limits the interpretation of the resultsthis is an open-label study,-there is a mismatch in the number of patients in refractory/recurrent ascites.

Singh et al. 2008	Midodrine Versus Alburnin in the Prevention of Paracentesis- Induced Circulatory Dysfunction in Cirrhotics: A Randomized Pilot Study	India	RCT	2005	2006	Presence of tense asciles requiring frequent therapoulic paracettesis – patients less than 10 yor of age: -also not a testial hypertension, a history of coronary least desses, cardade failurs, symptomalic a tentils, negatorost ministration and hepatic encephalopathy - absence of tespiss and gestorietterstal bedrefor within 7 days before the study - absence of recent use of diuretics, bela-blockers, plasma expanders, or paracentesis ¹		Not specified
Singh et al. 2012	Midodrine in patients with cirrhosis and refractory or recurrent ascites: A randomized pilot study	India	RCT	2007	2009	"Presence of refractory or recurrent asciles – patients less than 70 years of age -absence of gastrointesinal bleeding, hegaturmal oyndrom, hegate complaticipathy of grade 2 or higher or infection within 1 month preceding the study or during the study - presence of diabetes, intrinsic mart or cardiovascular diabetes, introduced and a study of the study diabetes and the study of the study of the presence of hegatocellular cardiovan or optial win thromosis - no treatment with drugs with known effects on systemic and remal hemodynamics within 7 days before inclusion."		Not specified
Singh et al. 2013	Midodrine and Clonidine in Patients With Cirrhosis and Refractory or Recurrent Ascites: A Randomized Pitot Study	India	RCT	2010	2011	"-Presence of refractory or recurrent ascless- patientises than 70 years of age; - absence of gastoristicssinal biederig, hepatorenal ayndrom, hepatei completiopathy of grade 2 or higher; or infection within 1 month precording the study or during the study - presence of diabetesis, infrinsic rend or cardiovascular disease, or arterial hypertension on history and physical examination; abnormal urine analysis, chest artidiograph, or discritory darge the study - thrombosis - no treatment with drugs with homone flection orspetimic and renal hemodynamics within 7 days before inclusion"	-	Not specified.
Solà et al. 2018	Midodrine &Albumin For Preventing Complications In Patients With Cirrhosis Awaiting Liver transplantation	Spain	RCT	August 2008	March 2015	*Age cider fhan 18 yr Cirthosis defined by standard clinical, analytical and/or hisbiogical ortesu Baterist in the walling ist for liver transplantation Acciles Written informed consent.*	"Arterial hypertension defined as systelic arterial pressure 350mm/kg andre diastelic arterial pressure 350mm/kg or drug therapy for arterial hypertension. Treatment with prothotopic drugs, transjoudin irritahepatia antibiotics within the last 7 days prot to study inclusion except for nofloxion or relativities as prophyticskis for SBP or recurrent Hic. respectively Chronic heat or respiratory failure; liade for combined lave-kideny transpint; pervisous her transpiratir".	Not specified.

TABLE 2: Supplementary file, basic details of included studies

Alsebaey et al. (2013) [14]; Appenrodt et al. (2006) [1]; Yosry et al. (2018) [4]; Bari et al. (2012) [15]; Hamdy et al. (2014) [16]; Hanafy et al. (2016) [6]; Kalambokis et al. (2005) [6]; Kalambokis et al. (2007) [17]; Minakari et al. (2011) [18]; Misra et al. (2010) [7]; Rai et al. (2016) [19]; Singh et al. (2015) [19]; Singh et al. (2012) [2] Singh et al. (2012) [20]; Singh et al. (2013) [2]; Solat et al. (2018) [2]

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info**: All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships**: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships**: All authors have declared that there are no within the submitted work. **Other relationships**: All authors have declared that there are no submitted work. **Other relationships**: All authors have declared that there are no submitted work. **Other relationships**: All authors have declared that there are no submitted work. other relationships or activities that could appear to have influenced the submitted work.

References

- Appenrodt B, Wolf A, Grünhage F, et al.: Prevention of paracentesis-induced circulatory dysfunction: midodrine vs albumin. A randomized pilot study. Liver Int. 2008, 28:1019-25. 10.1111/j.1478-3231.2008.01734.x
- Arroyo V, Ginès P, Gerbes AL, et al.: Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology. 1996, 23:164-76. 10.1002/hep.510230122
 Singh V, Dheerendra PC, Singh B, et al.: Midodrine versus albumin in the prevention of paracentesis-induced circulatory dysfunction in cirrhotics: a randomized pilot study. Am J Gastroenterol. 2008, 105:1399-
- 405. 10.1111/j.1572 0241.2008.01787.x 4. Yosry A. Soliman ZA, Eletreby R, Hamza I, Ismail A, Elkady MA: Oral midodrine is comparable to albumin
- Yosty A, Soliman ZA, Letterby K, Hamza J, Ismail A, Eikady MA: Oral midoarine is comparative to aloun infusion in cirribici patients with refractory assites undergoing large-volume parameterissi: results of a pilot study. Eur J Gastroenterol Hepatol. 2019, 31:345-51. 10.1097/MEG.000000000001277 Angeli P, Volpin R, Piovan D, et al.: Acute effects of the oral administration of midodrine, an alpha-adrenergic agonist, on renal hemodynamics and renal function in cirrbotic patients with ascites. Hepatology. 1998, 28:397-45. 10.1002/hep.510220407 5.
- 6. Hanafy AS, Hassaneen AM: Rifaximin and midodrine improve clinical outcome in refractory ascites including renal function, weight loss, and short-term survival. Eur J Gastroenterol Hepatol. 2016, 28:1455-61. 10.1097/MEG.0000000000743
- Wisra VL, Vuppalanchi R, Jones D, Hamman M, Kwo PY, Kahi C, Chalasani N: The effects of midodrine on the natriuretic response to furosemide in cirrhotics with ascites. Aliment Pharmacol Ther. 2010, 32:1044-50. 7. the nat
- 10.1111/j.1365-2036.2010.04426.x Kalambokis G, Economou M, Fotopoulos A, Al Bokharhii J, Pappas C, Katsaraki A, Tsianos EV: The effects of 8. chronic treatment with octroide versus octreotide plus indiddrine on systemic hemodynamics and renal hemodynamics and function in nonazotemic cirrhotic patients with ascites. Am J Gastroenterol. 2005, 100:879-85. 10.1111/j.1572 0241 2005 408
- Guo TT, Yang Y, Song Y, Ron Y, Liu ZX, Cheng G: Effects of midodrine in patients with ascites due to cirrhosis: Systematic review and meta-analysis. J Dig Dis. 2016, 17:11-9. 10.1111/1751-2980.12304
 Liberati A, Altman DG, Tetzaffi , et al.: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009,
- 339:b2700. 10.1136/bmj.b2700 Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia . (2021). Accessed: 11.
- Content e systematic review southers, versa rean minoration, neutodine, Australia (2021). Accessed May 15, 2021: http://www.condence.org.
 Mean Variance Estimation. (2021). Accessed: April 24, 2021: https://web.archive.org/web/20181224162602/http://www.comp.hkbu.edu.hk/~xwan/median2mean.html..

- 13. Sterne JA, Savović J, Page MJ, et al.: RoB 2: a revised tool for assessing risk of bias in randomised trials . BMJ. 2019, 366:14898, 10,1136/bmi,14898
- Jostina F, G. Vander, J. 1997, March 2014, State Control Contervice Control Control Control Control Control Control Contr

- 10.1016/j.lhep.2006.09.012
 Minakari M, Faiiaz L, Rowshandel M, Shavakhi A: Comparison of the effect of midodrine versus octreotide on hemodynamic status in cirrhotic patients with ascites. J Res Med Sci. 2011, 16:87–93.
 Rai N, Singi B, Singh A, Yigiyeergiya R, Sharma N, Bhalla A, Singh Y: Midorine and tolvaptan in patients with cirrhosis and refractory or recurrent ascites: a randomised pilot study. Liver Int. 2017, 37:406-14.
- with cirrhosis and refractory or recurrent ascites: a randomised pilot study. Liver Int. 2017, 37:406-14.
 10.1111/iiv.13250
 20. Singh V, Dhungana SP, Singh B, et al.: Midodrine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. J Hepatol. 2012, 56:348-54.
 10.1016/j.lhep.2011.04.027
 21. Singh V, Singh A, Singh B, Vijayvergiya R, Sharma N, Ghai A, Bhalla A: Midodrine and clonidine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. J Hepatol. 2012, 36:348-54.
 10.1016/j.lhep.2011.04.027
 21. Singh V, Singh A, Singh B, Vijayvergiya R, Sharma N, Ghai A, Bhalla A: Midodrine and clonidine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. Am J Gastroenterol. 2015, 108:550-7.10.1038/ajg.2015.9

- Sola E. Sole C., Sinón-Tatero M, et al.: Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. J Hepatol. 2018, 69:1250-9. 10.104/j.hep.2018.08.006
 Kalambodis GM, Tsianos EV: Vasoconstrictor therapy for patients with cirrhosis with ascites but without hepatorenal syndrome. Hepatology. 2008, 48:686. 10.1002/hep.22247
 Tandon P, Tsuyuki RT, Mitchell L, et al.: The effect of I month of therapy with midodrine, octreotide-LAR and albumin in refractory ascites: a pilot study. Liver Int. 2009, 29:169-74. 10.1111/j.1478-3231.308.01728 x 3231.2008.01778.x