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

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Abstract

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

Search Strategy

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", "portal hypertension", and suitable Boolean operators. Odds ratio (OR) and mean difference (MD) were used to analyze pool data as appropriate with a 95% confidence 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 (MD: 3.95 mmHg; 95% CI, 1.55-6.36) and MELD (Model for End-Stage Liver Disease) score (MD: -1.27; 95% CI, -2.49 to -0.04) compared to standard 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 SAP, plasma renin activity, plasma aldosterone concentration, MELD scores, 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 not 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.

Keywords:

Midodrine, ascites, cirrhosis, albumin, meta-analysis

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 therapeutic 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 than diuretic therapy in such cases [3]. Albumin, however, is expensive and, may have some risk of disease transmission, its use is thus controversial in some countries [1, 2]. Peripheral arterial vasodilation has been hypothesized to be the critical factor in the pathogenesis of functional renal abnormalities in patients with cirrhosis [1]. Venoconstriction administration may decrease arterial vasodilation caused by paracentesis and prevent complications associated with a decrease in the effective arterial blood volume. Midodrine, an alpha-1 agonist directly acting on peripheral alpha receptors, is a vasomotorist and is available as a cheap oral formulation. It has been commonly used to treat orthostatic hypotension and multiple secondary hypotensive disorders [4-6]. Recently, a single dose administration of midodrine has been shown to substantially improve the systemic and renal hemodynamics of ascites non-ascitic cirrhotic patients [7]. However, clinical trials evaluating Midodrine have provided inconsistent findings in patients with liver cirrhosis-related ascites, irrespective of the refractory status of the ascites [8-11].

We aimed 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 paracentesis/drainage, assessment of MELD (Model For End-Stage Liver Disease), plasma renin, aldosterone, and creatinine.

Methods

Protocol

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guideline was followed to carry out our systematic review and meta-analysis and is registered in PROSPERO (CRD420212232872) [12].

Eligibility Criteria

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 and one secondary outcome was reported. Studies like editorials, commentary, viewpoint, case reports and series, observational studies, and studies on animal or cell lines were excluded. In addition, articles with no proper data on midodrine on cirrhotic ascites and lacking adequate data of interest were excluded.

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", "portal hypertension", and suitable Boolean operators. The detailed search strategy is mentioned in the supplementary file.

Study Selection

Two reviewers (P 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 P and GM. Titles were extracted for both quantitative and qualitative synthesis. The studies were included by taking the third reviewer’s opinion (GM). All the screening was done with the help of Covidence [13].

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].
Study Quality

The quality of individual articles was evaluated using the Cochrane ROR (Risk of Bias) 2.0 for RCTs (13). 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](image)

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). Heterogeneity was measured by the I² 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 heterogeneity. 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 147 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.
Narrative summary

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 2/1,3,4,6-14,22.

| Study ID | Particulars | Intervention group | Comparator group |
|----------|-------------|--------------------|------------------|
|          | Year        | 2013               |                  |
|          | Study design| RCT                |                  |
|          | Total patients | 50                |                  |
|          | Description  | Oral midodrine (5–10 mg three times daily) | Standard-dose albumin (6 g/l ascitic fluid removed) Others intravenous terlipressin (3 mg), intravenous Hydroxyethyl Starch (HES) (9 g/l ascitic fluid removed), Low-dose albumin (2 g/l ascitic 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 |
|          |             | Serum creatinine(mg/dL) 0.92 ± 0.37 | 0.85 ±0.36 |
|          |             | 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 ± 1.09 |
|          |             | ΔSerum creatinine(mg/dL) 0.02 ± 0.23 | 0.06 ±0.29 |
|          |             | ΔUrine output (ml/min) 220.00 ± 490.96 | 468.00± 324 |
|          |             | ΔPRA (µU/ml) 30.75 ± 85.07 | 26.28 ± 30.20 |
|          |             | ΔAldosterone(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 patients | 24                |                  |
|          | Description  | Midodrine (12.5 mg post-paracentesis every 8 h for 2 days, six doses each) after the end of paracentesis | Albumin (2 g/L of removed ascites) with placebo pills |
Population characteristics

Participants

- Male (number/total): 11/13
- Female (number/total): 4/11

AGE mean

- T1: 52 (48;61)
- T2: 50 (48;63)

Weight (kg)

- T1: 67±11
- T2: 69±13

Baseline Values

- Volume of ascites removed (l): 7 (5.7; 10)
- MELD score: 11(8;14)
- MAP (mmHg): 77 (70;79)
- Serum creatinine (mg/dL): 0.98 (0.78;1.16)
- S-Na (mmol/L): 131 (128;133)
- Plasma renin (mU/ml): 677.5 (179.7;2016.3)
- PAC (pg/mL): 858 (743;1446)

Outcome

- Median values with IQR On day 6
  - MAP (mmHg): 80 (62;91)
  - Serum creatinine (mg/dL): 1.22±0.22
  - Creatinine clearance (ml/min): 68.73±20.72
  - Plasma renin (mU/ml): 133.5 (93.33;228.83)
  - PAC (pg/mL): 1266 (1043;2141)

Paracentesis Induced Circulatory Dysfunction (PICD)(number/total)

- T1: 6/11 (60%)
- T2: 4/13 (31%)

Renal impairment (number/total)

- T1: 2/11 (20%)
- T2: 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: (30 days midodrine) Midodrine 12.5 mg every 8 h for 30 days after LVP

Regular dose of albumin (8 g for each liter of removed ascitic fluid) immediately after LVP

Population characteristics

Participants

- Male (number/total): 25/25
- Female (number/total): 10/25

Age

- T1: 51.36±11.68
- T2: 50.48±7.93

weight(kg)

- T1: 80.04±8.75
- T2: 80.16±9.26

Baseline Values

- Volume of ascites removed (l): 5.80±0.92
- Na (mEq/l): 132.68±3.34
- Creatine (mg/dL): 1.22±0.22
- Urinary Na (mEq/L): 26±13

Outcome on Day 6 (Presented in mean ±SD/ median(IQR)

- MAP
  - T1: 82.2±5.06
  - T2: 78.47±4.22
- Serum creatinine
  - T1: 1.35±0.32
  - T2: 1.24±0.20
- Creatinine clearance
  - T1: 68.73±20.72
  - T2: 77.03±20.93

on Day 30

- MAP
  - T1: 80.87±4.41
  - T2: 76.58±3.32
- Serum creatinine
  - T1: 1.38±0.42
  - T2: 1.30±0.53
- Creatinine clearance
  - T1: 70.96±23.47
  - T2: 68.73±20.72
- Urinary Volume
  - T1: 66.73±20.72
  - T2: 77.03±20.93

30 Day mortality:

- T1: 0
- T2: 2

Year

2012

Study design

RCT

Total participants

25

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### Bari et al. (2012)

| Description | Saline solution (albumin placebo) | Ondtareotide 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 (albumin placebo) every month | Midodrine placebo 3 times a day |
|-------------|----------------------------------|-----------------------------------------------|---------------------------------|------------------------------------------|-----------------------------------|-------------------------------|

#### Population characteristics
- **Participants**: 12/13
- **Male (number/total)**: 12/12
- **Female (number/total)**: 0/3

#### Baseline Values
- **Amount of ascites removed**: 6–10.5 vs 5–8.5
- **Creatinine level (mg/dL)**: 1.1 (0.9–1.5) vs 1.1 (0.9–1.5)
- **MELD score**: 14 (13–16) vs 17 (11–20)
- **Serum aldosterone level (ng/dL)**: 42 (12–100) vs 38 (18–89)
- **PRA (ng/mL/hr)**: 11.7 (7.9–25.1) vs 19 (17.4–34.5)

#### Outcome on Day 6
- **Serum Creatinine**: 1.2 (1.0–1.8) vs 0.9 (0.9–1.4)
- **MELD score T**: 15 (12–16) vs 14 (10–16)
- **Change in PRA**: -7.1 (-22 to 67) vs 1.3 (-51 to 40)
- **Change in MAP**: -2 (-7 to 5) vs -1.3 (-7 to 2)

#### Patients who developed PICD
- **2/8 vs 2/11**

#### 10 months mortality
- **5/12 vs 4/13**

### Hamdy et al. (2014)

| 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
- **Female (number/total)**: 8/25

#### Baseline Values
- **MELD score**: 15.3 ± 4.3 vs 15.0 ± 3.8
- **Ascitic fluid removed (L)**: 6.8 ± 0.7 vs 6.9 ± 1.0
- **Serum albumin (g/dL)**: 2.3 ± 0.4 vs 2.6 ± 0.5
- **MAP (mmHg)**: 78.9 ± 5.5 vs 81.3 ± 8.1
- **Serum creatinine (mg/dL)**: 0.9 ± 0.2 vs 1.1 ± 0.2
- **Plasma renin (ng/ml/h)**: 3.0 ± 0.3 vs 4.1 ± 0.9
- **PAC (pg/mL)**: 166.7 ± 64.2 vs 204.8 ± 115.9

#### Outcome
- **On day 6**: MAP (mmHg) 71.9 ± 5.8 vs 71.3 ± 7.8
- **Serum creatinine (mg/dL)**: 0.99 ± 0.2 vs 1.10 ± 0.2
- **PRA (ng/mL/hr)**: 4.2 ± 0.7 vs 4.11 ± 0.74
- **PAC (pg/mL)**: 266.8 ± 130.8 vs 177.6 ± 100.5

#### Adverse outcomes
- **HRS (number/total)**: 9/25 vs 0
- **Death rate (number/total)**: 7/25 vs 0

### Shrestha et al. (2016)

| 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 amiodine 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)**: 303/200
- **Female (number/total)**: 97/200

#### Baseline Values
- **MAP (mmHg)**: 75.8 ± 6.2 vs 77 ± 6.5
| Hanafy et al. (2016) | Weight (kg) | 84.4 ± 8 | 80.3 ± 4.7 |
| | Creatinine (mg/dL) | 1.5 ± 0.2 | 1.4 ± 0.2 |
| | Creatinine clearance (mL/min) | 86.4 ± 11 | 71.3 ± 14.2 |
| | U-Na (mg/24 h) | 16.5 ± 3.6 | 17.2 ± 2.2 |
| | Urine output (mL/24 h) | 528.6 ± 101 | 580 ± 130 |
| | PRA (ng/ml/h) | 4.5 ± 1.2 | 3.9 ± 0.9 |
| | PAC (ng/dL) | 21.6 ± 5.6 | 19 ± 3.7 |
| | MELD | 22.7 ± 2 | 22.1 ± 2.4 |
| Kalambokis et al. (2005) | | | |
| | Year | 2005 | 2007 |
| | Study design | RCT | RCT |
| | Total participants | 25 | 20 |
| | Description | Octreotide 300 µg, b.i.d. combined with midodrine hydrochloride 7.5 mg, t.i.d. subcutaneous octreotide alone | Oral midodrine 10 mg. t.i.d. for 7 days. 10 mg. t.i.d. Placebo for 7 days |
| | Baseline Values | MAP (mmHg) | 79.4 (74-82.6) | 79 (70.4-86.2) |
| | | Cardiac Output (L/min) | 6.5 (5.8-6.2) | 6.2 (5.8-6.9) |
| | | Weight (kg) | 70.5 (69.5-73) | 68 (65-64) |
| | | Serum creatinine (mg/dL) | 0.9 (0.7-1) | 0.8 (0.7-1) |
| | | U-Na (mg/24 h) | 22 (16.5-40.2) | 21 (14-48.8) |
| | | Urine output (mL/24 h) | 0.97 (0.79-1.11) | 0.86 (0.5-1.05) |
| | | PRA (µU/ml) | 109.9 (81.3-183.8) | 66 (22-148.8) |
| | | PAC (ng/dL) | 82.5 (40.3-144) | 38.4 (15.3-91.9) |
| | Outcome on day 10 | MAP (mmHg) | 80.6 (70.7-83.3) | 82.1 (77.5-94.3) |
| | | Cardiac Output (L/min) | 6.8 (6.4-7.2) | 6.5 (6.2-6.2) |
| | | Serum creatinine (mg/dL) | 0.9 (0.7-1.1) | 0.8 (0.7-1.1) |
| | | U-Na (mg/24 h) | 17.1 (11.43) | 26.7 (18.5-47.3) |
| | | Urine output (mL/min) | 0.83 (0.74-0.92) | 1.11 (0.76-1.59) |
| | | PRA (µU/ml) | 28.6 (17.3-110.5) | 31.8 (6.7-64.6) |
| | | PAC (ng/dL) | 19.9 (17.6-103.8) | 11.1 (3.3-47.7) |
| | Year | 2007 | 2005 |
| | Study design | RCT | Study design |
| | Total participants | 20 | 25 |
| | Description | Oral midodrine 10 mg, t.i.d. for 7 days. 10 mg, t.i.d. Placebo for 7 days | Dry Calamine 300 µg, b.i.d. combined with midodrine hydrochloride 7.5 mg, t.i.d. |
| | Population characteristics | Participants | 13 | 12 |
| | | Male (number/total) | 7/13 | 6/12 |
| | | Female (number/total) | 6/13 | 6/12 |
| | | Age mean | 54 (40-77) | 56 (43-75) |
| | Kalambokis et al. (2005) | Baseline Values | MAP (mmHg) | 79.4 (74-82.6) | 79 (70.4-86.2) |
| | | Cardiac Output (L/min) | 6.5 (5.8-6.2) | 6.2 (5.8-6.9) |
| | | Weight (kg) | 70.5 (69.5-73) | 68 (65-64) |
| | | Serum creatinine (mg/dL) | 0.9 (0.7-1) | 0.8 (0.7-1) |
| | | U-Na (mg/24 h) | 22 (16.5-40.2) | 21 (14-48.8) |
| | | Urine output (mL/24 h) | 0.97 (0.79-1.11) | 0.86 (0.5-1.05) |
| | | PRA (µU/ml) | 109.9 (81.3-183.8) | 66 (22-148.8) |
| | | PAC (ng/dL) | 82.5 (40.3-144) | 38.4 (15.3-91.9) |
| | Outcome on day 10 | MAP (mmHg) | 80.6 (70.7-83.3) | 82.1 (77.5-94.3) |
| | | Cardiac Output (L/min) | 6.8 (6.4-7.2) | 6.5 (6.2-6.2) |
| | | Serum creatinine (mg/dL) | 0.9 (0.7-1.1) | 0.8 (0.7-1.1) |
| | | U-Na (mg/24 h) | 17.1 (11.43) | 26.7 (18.5-47.3) |
| | | Urine output (mL/min) | 0.83 (0.74-0.92) | 1.11 (0.76-1.59) |
| | | PRA (µU/ml) | 28.6 (17.3-110.5) | 31.8 (6.7-64.6) |
| | | PAC (ng/dL) | 19.9 (17.6-103.8) | 11.1 (3.3-47.7) |
| | Year | 2007 | 2005 |
| | Study design | RCT | Study design |
| | Total participants | 20 | 25 |
| | Description | Oral midodrine 10 mg, t.i.d. for 7 days. 10 mg, t.i.d. Placebo for 7 days | Dry Calamine 300 µg, b.i.d. combined with midodrine hydrochloride 7.5 mg, t.i.d. |
| | Population characteristics | Participants | 13 | 12 |
| | | Male (number/total) | 7/13 | 6/12 |
| | | Female (number/total) | 6/13 | 6/12 |
| | | Age mean | 54 (40-77) | 56 (43-75) |

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| Kalambokis et al. (2007) | Baseline Values |
|-------------------------|----------------|
| MAP (mmHg)              | 84.4 ± 11.9    |
| CIcre (L/min/m²)        | 84.4 ± 14.3    |
| Urea (mg/dL)            | 26.6 ± 14.8    |
| UV (liter/m²/day)       | 0.58 ± 0.26    |
| PRA (ng/mL/h)          | 8.55 ± 4.24    |
| PA (mg/dL)              | 206 ± 101      |
| Outcome on 7 days       |
| MAP (mmHg)              | 82.8 ± 10.5    |
| CIcre (L/min/m²)        | 89.5 ± 12.9    |
| Urea (mg/dL)            | 23.7 ± 15.5    |
| UV (liter/m²/day)       | 0.93 ± 0.41    |
| PRA (ng/mL/h)          | 8.2 ± 3.98     |
| PA (mg/dL)              | 340 ± 83       |

| Minakari et al. (2011) | 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|
| Female(number/total)   | 5/17 | 3/17 |
| Age mean (years)       | 59.47 ± 14.08 | 49.59 ± 18.03 |
| Baseline Values        |
| PRA (ng/ml/h)          | 20.99 ± 10.93 | 28.32 ± 8.65 |
| MAP (mmHg)             | 73.84 ± 10   | 78.43 ± 8.13 |
| Weight (kg)            | 67.47 ± 11.25 | 85.19 ± 7.9 |
| Outcome on day 4 (mean ± SD) |
| PRA (ng/ml/h)          | 12.94 ± 7.62 | 20.64 ± 8.23 |
| MAP (mmHg)             | 81.57 ± 11.25 | 85.19 ± 7.9 |

| Misra et al. (2010)    | Year | 2010 |
|------------------------|------|------|
| Study design           | RCT  |      |
| Total participants     | 15   |      |
| Description            | Midodrine 15 mg PO and furosemide 40 mg IV intravenously, Placebo (orally given 30 min before) and furosemide 40 mg intravenously |
| Population characteristics |
| Participants           | 17   |      |
| Male(number/total)     | 12/17|      |
| Female(number/total)   | 5/17 |      |
| Age mean (years)       | 52.7 ± 7.6 |      |
| MELD (score)           | 12.14 ± 2.5 |      |
| Weight (kg)            | 80.7 ± 14 |      |
| Systolic blood pressure (mmHg) | 114 ± 15.4 |      |
| Serum albumin (g/dL)   | 3.6 ± 0.5 |      |
| Serum creatinine (mg/dL) | 1.05 ± 0.2 |      |
| Outcome 0-6 hour       |
| Total urine volume (mL) | 1770 ± 262 | 1962 ± 170 |
| Total urinary sodium (mMol) | 109 ± 42 | 126 ± 69 |

| Shrestha et al. (2016)  | 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 diuretics (spironolactone 100-400mg/day) was given with dose escalation by one step at a time permitted for a >10-pound weight gain-and-repeated large volume paracentesis (LVP) |
| Population characteristics |
| Patients               | 13   | 12   |
| Male(number/total)     | 8/13 | 11/12|
| Female(number/total)   | 5/13 | 1/12 |
| Weight (kg)            | 70.0 ± 10.1 | 66.4 ± 11.4 |
| MELD score             | 4.5 ± 2.3 | 1.1 ± 2.5 |
| Outcome on 1 month | MAP | 80.5±4.6 | 84.5±7.1 |
|-------------------|-----|----------|----------|
|                   | CO  | 5.8±0.20 | 5.8±0.33 |
|                   | Ura| 70.3±32.2 | 56.8±22.4 |
|                   | PRA| 11.7±2.5  | 13.8±2.8 |
|                   | 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 at 3 months | MAP | 90.3±3.6 | 83.7±7.6 |
|---------------------|-----|----------|----------|
|                     | CO  | 5.7±0.22  | 5.7±0.33 |
|                     | U-Na| 111.2±26.9 | 79.6±10.5 |
|                     | PRA | 8.5±1.4   | 13.8±2.8 |
|                     | PA  | 1147.6±316.7 | 1527.5±300.2 |
|                     | Serum Creatinine | 0.84±0.19 | 0.83±0.10 |
|                     | Urine Output | 1.44±0.27 | 1.25±0.23 |

| Singh et al. (2008) | Year | 2012 |
|---------------------|------|------|
| Study design        | RCT  | RCT  |
| Total participants  | 40   | 40   |
| Description         | Midodrine 5–10 mg three times a day | Albumin 8 g/L of ascitic fluid was removed (mean 48.4 ± 12.1 g) |
| Population characteristics | Participants | 20 | 20 |
|                       | Male (number/total) | 18/20 | 17/20 |
|                       | Female (number/total) | 2/20 | 3/20 |
| Age mean ±SD         | 48.15 ± 11.26 | 45.05 ± 14.16 |
| Baseline Values      | MAP  | 86.10 ± 6.90 | 85.85 ± 6.63 |
|                     | U-Na | 9.60±12.42 | 18.80±29.75 |
|                     | PRA  | 44.44±8.44  | 43.18±10.73 |
|                     | PA   | 1,640.00±539.40 | 1,890.00±590.18 |
| Serum Creatinine     | 0.79±0.17 | 0.85±0.17 |
| Urine Output (ml/day) | 1,495.00 ± 337.91 | 1,540.00 ± 440.57 |

| Outcome Day 6 | MAP  | 87.30 ± 7.36 | 87.50 ± 7.23 |
|               | U-Na | 25.00 ± 23.38 | 22.55 ± 28.65 |
|               | PRA  | 41.39 ± 10.21 | 45.90 ± 8.59 |
|               | PA   | 1,705.00 ± 493.11 | 1,985.00 ± 497.65 |
| Serum Creatinine | 0.79±0.17 | 0.85±0.17 |
| Urine Output (ml/day) | 1,640.00 ± 388.52 | 1,555.00 ± 527.63 |
| Output (ml/day)  | 1,640.00 ± 388.52 | 1,555.00 ± 527.63 |
| PICO (number/total) | 0 | 0 |
| Death (number/total) | 0 | 0 |

| Response rate | Repeat paracentesis (within 3 month of treatment) (number/total) | 1/20 | 2/20 |
|---------------|------------------------------------------------------------------|------|------|
|               | Year                                                            | 2012 |      |
|               | Study design                                                    | RCT  |      |
|               | Total participants                                              | 40   |      |

Midodrine Subjects: SMT - restriction of sodium - treatment with diuretics
Singh et al. (2012)

**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 gain and -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 ± 10.04 | 47.6 ± 11.033 |

**Baseline Values**

| Recurrent ascites(number/total) | 14/20 | 14/20 |
| 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 | 82.59 ± 11.44 |
| CD | 5.68 ± 1.86 | 5.81 ± 1.82 |
| Serum Sodium | 134.6 ± 10.04 | 134.15 ± 5.5 |
| Ura | 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 ± 0.27 | 0.84 ± 0.205 |
| Urine Output | 1235 ± 665.12 | 1381.2 ± 636.8 |

**Outcome on 1 month**

| Weight | 67.15 ± 19.78 | 65.5 ± 18.70 |
| MELD Score | 13.9 ± 4.1 | 16.1 ± 5.6 |
| MAP | 92.88 ± 7.91 | 90.16 ± 8.5 |
| Ura | 90.21 ± 32.19 | 88.73 ± 18.93 |
| PRA | 0.85 ± 2.51 | 14.73 ± 2.48 |
| PA | 921.5 ± 547.8 | 1440.59 ± 497.3 |
| Serum Creatinine | 0.84 ± 0.20 | 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 2 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 |

Shrestha et al. (2012)
| Singh et al. (2013) | Solà et al. (2018) |
|------------------|------------------|
| **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** | 13.5 ± 5.71 | 13.92 ± 4.18 |
| **MAP** | 85.3 ± 8.72 | 92.6 ± 6.06 |
| **CD** | 6.67 ± 1.21 | 6.70 ± 1.36 |
| **Urea** | 42.2 ± 12.6 | 35.6 ± 14.3 |
| **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 | 1526.0 ± 497.1 |
| **Outcome on 1 month** | 1/15 | 1/15 |
| **MELD Score** | 12.4 ± 3.67 | 13.5 ± 3.99 |
| **MAP** | 94.7 ± 4.48 | 87.6 ± 5.24 |
| **Urea** | 52.3 ± 19.6 | 45.2 ± 19.6 |
| **Serum Creatinine** | 1.01 ± 0.25 | 1.13 ± 0.22 |
| **Urine Output (mL/day)** | 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)** | - | - |
| **Response Rate:** | - | - |
| **Total patients** | 14 | 12 |
| **Complete (number/total)** | - | - |
| **Partial (number/total)** | 11/14 | 5/12 |
| **None (number/total)** | - | - |
| **Year** | 2018 | 2018 |
| **Study design** | RCT | RCT |
| **Total participants** | 173 | 173 |
| **Description** | Methylprednisolone 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±10 81±10
- **Serum creatinine (mg/dL)** 0.96±0.3 1.0±0.4
- **MAP (mmHg)** 80±10 81±10

**Outcome**
- **All Week 4, MELD score** 13±4 13±4
- **All Week 12, MELD score** 13±3 13±4
- **All Week 24, MELD score** 13±2 12±4
- **Patients with adverse event (number/total)** 83/87 84/86
- **Renal impairment** 12±3 11±4
- **Hypotension** 11±2 14±4
- **Hepatic encephalopathy** 24±3 21±4
- **Sepsis** 12±3 13±4
- **Gastrointestinal bleeding** 8±3 4±4
- **Mortality at 2 month** 36±7 31±8
- **Mortality at 4 month** 68±7 51±8

**TABLE 1: Narrative summary of included studies**

| Abbreviations: ALT= Alanine transaminase, AST= Aspartate transaminase, BUN= Blood urea nitrogen, C= Control group, CO/ hr= Cardiac output, CTP score= Child-Turcotte-Pugh score; EF= Ejection fraction, F= Female, GCRC= General Clinical Research Center, GFR= serum creatinine clearance rate; HBP= Hypertensive brain stem; HCC= Hepatocellular carcinoma, HBV= Hepatitis B virus, HCV= Hepatitis C virus, HE= Hepatic encephalopathy, HR= Heart rate, INR= International normalized ratio, IQR= Interquartile range, IV= Intravenous, M= Male, MAP (mmHg)= Mean Arterial Pressure, MELD score= Model End Stage Liver Disease score, N= Total number, PAC/PA(pg/mL)= Plasma aldosterone concentration, PICD/PCD= Paracentesis Induced Circulatory Dysfunction, PO= Per-oral, PRA(ng/mL/h)= Plasma renin activity, SAAG= serum-ascites albumin gradient, SBP= Spontaneous bacterial peritonitis, SMT= Standard medical therapy, S-Na(mEq/L)= Serum Sodium, SVR(dynes/s/cm5)= Systemic vascular resistance, T= Treatment group, UGI= Upper gastrointestinal, U-Na(mEq/24 h)= Urinary sodium, UV= Urinary volume. |
Quantitative Analysis

Fourteen studies [1,3,4,6,8,14-22] 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; 95% 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; I² = 9%) (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. [1,3,4,6,8,14-22].

**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% CI -2.49 to -0.04; n= 868; I² = 73%) (Figure 4).

**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 -3.49, 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 339.55; P=0.84) (Figure 6).

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, 0.13 to 2.01; P=0.34 and OR, 2.05; 95% CI, 0.38 to 11.04; P=0.40 respectively) (Figure 7).
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 0.03; 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 8).

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; I² = 0%) (Figure 9).

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).
Discussion

Cirrhotic ascites is usually associated with hypotension due to vasodilation mediated by low effective 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 mortality and morbidity benefits. In this meta-analysis, we focused on the role of midodrine 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 in patients receiving midodrine compared to standard medical treatment as a potential effect of alpha-1 mediated vasoconstriction. Midodrine use was statistically significant in boosting serum creatinine compared to albumin, however, reduction in creatinine did not reach the level of significance when compared with SMT/placebo. This is likely due to the effect of midodrine, which has been found to improve 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, 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 bleeding, hypotension, and sepsis as some of the adverse effects of midodrine compared to placebo [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 onits and albumin are significant because midodrine is available in cheap oral formulation making it much easier to use.

Our study has several limitations. The endpoints for assessment of our outcomes were variable ranging from day one, day four, day 10, one month to three months [1,15-21]. In some of the studies, patients received concurrent adjuvant treatment like oestriol [1,15] and minocycline [1]. Another significant limitation was the wide variation in the dosage and duration of midodrine ranging from three days to one-month, 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 IFM 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

Supplementary file 1. Electronic database search details

| Published | Hits | Search: "midodrine" AND "ascites" AND "cirrhosis" |
|-----------|------|--------------------------------------------------|
| PubMed    | 242  | [Link: https://www.ncbi.nlm.nih.gov/pubmed?term=%22midodrine%22+%22ascites%22+%22cirrhosis%22] |
| Embase    | 525  | [Link: https://www.embase.com/efbm先进搜索结果页面/history.15/page.1?st1=%22midodrine%22+AND+%22ascites%22+AND+%22cirrhosis%22] |
| Scopus    | 255  | [Link: https://www.scopus.com/results/results.uri?Search: "midodrine" AND "ascites" AND "cirrhosis"] |

\*Note: All databases were searched on November 10, 2022.

Study ID | Title | Country | Design | Start date | End date | Inclusion criteria | Exclusion criteria | Limitations |
|---------|-------|---------|--------|------------|----------|------------------|-------------------|-------------|
| Sartory et al. 2013 | Prevention of paracentesis-induced circulatory dysfunction caused by other albumin alternatives | Egypt | RCT | 2013 - | | The presence of tense ascites determined by ultrasonography and abdominal ultrasound, requiring frequent therapeutic paracentesis, age younger than 65 years and older than 55 years, and absence of arterial hypertension, history of coronary disease, cerebrovascular disease, hepatic encephalopathy, hepatitis, ascites, bacteria peritonitis (defined by polymorphonuclear cell count >10 000/L or clinical examination, elevated creatinine concentration higher than 1.4 mg/dl, and gastrointestinal bleeding within 7 days before the study) | Not Specified | Not Specified |
| Appenzeller et al. 2016 | Reduction in the occurrence of paracentesis-induced circulatory dysfunction | Germany | RCT | October 2014 | May 2015 | The presence of fluid in ascites (HL), determined by abdominal ultrasound and peritoneal aspiration, requiring therapeutic paracentesis | Patients with a prothrombotic time of ≤60 s, patients with a platelet count of < 150 000/µL, a serum creatinine concentration of >1.5 mg/dl, ascites, patients with >10 000 polymorphonuclear cell count >10 000/L, a serum creatinine concentration of >1.4 mg/dl, age younger than 65 years and older than 55 years, and absence of arterial hypertension, history of coronary disease, cerebrovascular disease, hepatic encephalopathy, hepatitis, ascites, bacteria peritonitis (defined by polymorphonuclear cell count >10 000/L or clinical examination, elevated creatinine concentration higher than 1.4 mg/dl, and gastrointestinal bleeding within 7 days before the study) | Small sample size, the dose and duration of drug administration were fixed with no adaptation by pharmacokinetic parameters |
| Wanyi et al. 2016 | Outcomes in inpatient and outpatients with cirrhotic ascites undergoing paracentesis: interim analysis results of a pilot study | Egypt | RCT | April 2015 | May 2015 | | Patients with hepatic lymphoid obstruction | Not specified |

*Note: All studies were conducted between 2008 and 2016.*
| Reference | Study Design | Intervention Details | Patient Population | Results/Outcomes |
|-----------|--------------|----------------------|-------------------|-----------------|
| Shrestha et al. 2022 | RCT | Midodrine and octreotide plus Rifaximin | Cirrhosis patients with refractory ascites | Rifaximin and octreotide superior to midodrine in improving refractory ascites outcomes in cirrhotic patients without ascites. |
| Hamdy et al. 2012 | RCT | Comparison of octreotide plus diuretics vs. placebo | Patients with refractory ascites | The effects of octreotide plus diuretics vs. placebo on refractory ascites were not significant. |
| Kalambokis et al. 2016 | placebo-controlled trial | Midodrine vs. placebo | Patients with cirrhosis and refractory ascites | Midodrine was superior to placebo in improving refractory ascites outcomes. |

**Table Notes:**
- **RCT:** Randomized controlled trial
- **Greece:** Country of study location
- **India:** Country of study location
- **Iran:** Country of study location
Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/infrastructure: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors declare 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 declare that there are no other relationships or activities that could appear to have influenced the submitted work.

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