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Effects of Midodrine Among Cirrhotic Patients Undergoing Large-Volume Paracentesis: A Meta-Analysis

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Ascites; Midodrine; Chronic liver disease; Paracentesis-induced circulatory dysfunction

1. Abstract

1.1. Background and Objectives: The development of ascites among patients with liver cirrhosis is associated with poor prognosis and quality of life. Ascites refractory to diuretic use is usually treated with Large Volume Paracentesis (LVP), a procedure that may cause Paracentesis-Induced Circulatory Dysfunction (PICD). While human albumin is known to prevent PICD, its use is largely limited due to cost. The vasoconstrictor midodrine has been shown in some studies to be a viable alternative to albumin, although results are conflicting in some. This meta-analysis aims to assess the efficacy of midodrine on mortality and prevention of PICD compared to albumin among cirrhotic patients undergoing large-volume paracentesis.

1.2. Methods: We thoroughly searched literature on major databases. Studies fulfilling the inclusion and exclusion criteria were assessed using the Cochrane Risk of Bias Tool. Primary outcomes of interest included all-cause mortality and occurrence of PICD. Secondary outcomes were development of hyponatremia and acute kidney injury.

1.3. Results: Meta-analysis of four studies with a total of 164 patients showed no significant difference in all-cause mortality among cirrhotic patients who underwent large-volume paracentesis and were treated with midodrine compared to those who were given albumin infusion [RR 2.44 (95% CI 0.40-14.98) p = 0.33 I^2 31%]. No significant differences were seen in the occurrence of PICD [RR 0.95 (95% CI 0.14-6.56) p = 0.17], hyponatremia [RR 1.74 (95% CI 0.10-29.48) p = 0.70] and acute kidney injury [RR 3.07 (95% CI 0.33-28.27) p = 0.32].

1.4. Conclusions: The use of midodrine showed no statistically significant difference in mortality and PICD when compared to albumin. This medication may be a viable alternative in low-resource settings, however, the presence of heterogeneity and imprecision produces the certainty of this evidence.

2. Introduction

The development of ascites, or the abnormal fluid accumulation in the abdominal cavity, is a main complication of cirrhosis, occurring in about 60% of patients with cirrhosis. It is associated with poor prognosis, poor quality of life and high mortality especially in the case of refractory ascites [1].

At present, the main pathogenesis for ascites is not clear, however the leading theory is portal hypertension leads to splanchnic vasodilation, leading to systemic vasodilation. This leads to a decrease in effective blood causing activation of the renin-angiotensin-aldosterone system (RAAS). This subsequently causes renal sodium and water retention as well as hepatorenal syndrome [2].

Ascites is classified into uncomplicated and refractory in patients with cirrhosis. Refractory ascites is defined as ascites that does not decrease despite use of diuretic treatment and sodium restriction or early recurrence after large volume paracentesis [3]. For patients with massive or refractory ascites, large volume paracentesis is the therapeutic management of choice, followed by administration of diuretics and sodium diet restriction. However, all patients with refractory ascites should be considered for liver transplantation [4]. LVP is relatively a low-risk procedure in that there are few absolute contrain-

dications in its performance and the most dangerous side effect is probably Paracentesis-Induced Circulatory Dysfunction (PICD).

PICD was first described by Gines et al in 1988 among cirrhotic patients with tense ascites who underwent repeated LVP who did not receive intravenous albumin treatment.[7] It has since been defined biochemically with increased renin concentration in blood plasma of more than 50% from baseline values or exceeds 4ng/mL/hr in the first 5 days after LVP [5]. Occurrence of PICD is associated with higher incidence of renal failure, dilutional hyponatremia and increased overall mortality [2]. Albumin infusion has been recommended by the European Association for the Study of the Liver to prevent PICD based on multiple clinical trials over the years [6]. However, albumin remains to be costly and difficult to procure in low-resource settings.

It was previously thought that PICD occurs due to rapid fluid shifts after paracentesis resulting in decreased effective circulating plasma volume [9]. A later study, however demonstrated that 5-liter paracentesis on with portal hypertension-related ascites was not associated with a decrease in circulating plasma volume [10]. A decrease in systemic vascular resistance secondary to accentuation of arteriolar vasodilation was then demonstrated to be the predominant pathophysiologic process in PICD [11].

Midodrine is a prodrug that is enzymatically hydrolyzed to desglymidodrine, a selective alpha-1 receptor antagonist which causes vascular smooth muscle constriction; it is commonly used as treatment for orthostatic hypotension [13]. Its use among cirrhotic patients was first explored in 1998 by Angeli et al where it was observed that midodrine caused an increase in systemic vascular resistance with a possible preferential effect in the splanchnic circulation, as well a marked suppression of the plasma renin activity.[12] Several randomized controlled trials [14-17] compared the efficacy of midodrine in preventing PICD compared to albumin among cirrhotic patients undergoing LVP, albeit with dissimilar conclusions.

3. Objectives

The aim of this meta-analysis was to evaluate the efficacy of midodrine compared to albumin in 1) reducing all-cause mortality, and 2) preventing paracentesis-induced circulatory dysfunction among cirrhotic patients undergoing large-volume paracentesis. Secondary outcomes that would be analyzed included development of hyponatremia and acute kidney injury.

4. Methods

4.1. Literature Search Strategy

A sensitive search strategy was used for identifying randomized controlled trials. Electronic searches were completed in PUBMED, MEDLINE, Cochrane Central Register of Controlled Trials, and Google Scholar. The reference list of all identified papers were searched for further information.

The search strategy combined the search terms in Cochrane: "ascites" in title, abstract, keywords AND "Cirrhosis", "Midodrine", "Paracentesis induced circulatory dysfunction" and "Randomized Controlled Trial" in Search All Text in the Trials. The summary of the search strategy is demonstrated in (Figure 1).

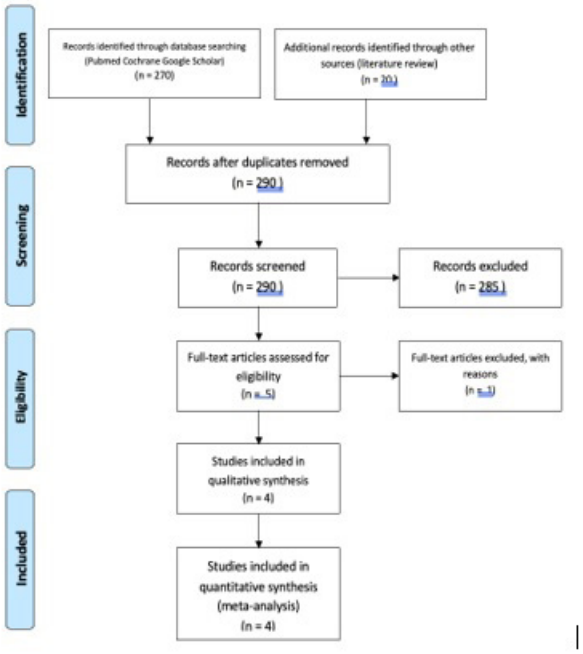

Figure 1: PRISMA flow chart showing the inclusion and exclusion of articles. Effects of midodrine among cirrhotic patients undergoing large-volume paracentesis: a meta-analysis

4.2. Study Eligibility Criteria

4.2.1. Inclusion Criteria: Studies that met the following criteria were included: 1) randomized control trials, 2) comparing midodrine and albumin, 3) included adult patients with cirrhosis with ascites, 4) should have reported data on at least one of the primary outcomes (occurrence of PICD, mortality).

4.2.2. Exclusion Criteria: Studies that were excluded were 1) study population or trial size was not clear, 2) non-RCT, qualitative study or study without extractable data, 3) types of publication was only reported in abstract form, 4) outcomes are others not specified in the inclusion criteria.

4.2.3. Data Extraction and Critical Appraisal: The following data were extracted and tabulated: type of study, year(s) of conduction and publication, country, baseline demographics of participants, preventive and therapeutic regimens, duration of treatment, number of patients allocated and outcomes using an intention-to-treat principle.

The two reviewers independently assessed the quality of the studies based on the criteria provided in the Cochrane Risk of Bias Assessment Tool version 2. Studies were assessed as high-quality or low risk of bias if a) treatment allocation was randomized and adequate concealment was done, b) treatment and control groups were balanced, c) outcome assessment was blind to both the investigator and participant, d) outcome detection methods were similar for both groups,

e) treatment and control groups were treated equally in terms of other therapeutic and co-interventions received, and f) intention to treat analysis was conducted. If there were unclear or no details mentioned in the study, they were assigned with an unclear risk or high risk for bias depending on what was unclear in the study.

The primary outcomes of interest were the occurrence of PICD and mortality in each study, while secondary outcomes included the occurrence of hyponatremia and acute kidney injury. The definitions used for these discrete outcomes were as follows:

- **Mortality** - death from any cause occurring during the study period
- **PICD** - increase in the plasma renin concentration by >50% from pretreatment value at day 5-6 after LVP
- **Hyponatremia** - post-treatment serum sodium less than 130 mEqs/L, OR decrease by 5 mEqs/L if the baseline value is less than 130 mEqs/L
- **Acute kidney injury** - increase in serum creatinine to more than 1.5 mg/dL, OR an increase by more than 50% of baseline value
- Baseline and post-treatment data for plasma renin activity, serum sodium and serum creatinine were also obtained if they were available.

5. Data Synthesis and Statistical Analysis

Pooled analysis using the random effects model to obtain a risk ratio for binary outcomes was done using Review Manager (RevMan) Version 5.4. A 95% confidence interval was used and a P value < 0.05 was assumed to show a statistically significant difference. A forest plot was constructed to show the overall effect of the intervention. Continuous variables of interest were also extracted from the included studies. Change-from-baseline values were generated from available data in the studies. Sample data that were reported as median and interquartile ranges were converted to mean and standard deviations using a calculator by Wan et al [18]. Post-treatment standard deviations that were not reported in the papers were also imputed using a formula by Zhang et al [19]. For each parameter of interest (serum sodium, serum creatinine, plasma renin), a forest plot was constructed to summarize the effect of each intervention. Another forest plot was generated to show mean differences between the two groups. Standardized mean difference was used for parameter/s with differing unit of measurements across the included studies.

Heterogeneity was evaluated using the chi square test with p value < 0.10 as the cut-off for significant heterogeneity. Additionally, the I^2 statistic was used to assess the degree of heterogeneity, using a cutoff for significant heterogeneity as 50%.

6. Results

6.1. Literature Search

After thoroughly searching PUBMED, the Cochrane Central Register of Controlled Trials (CENTRAL), a total of 290 studies were identified in addition to manual searches. After screening, 285 studies were excluded as they were irrelevant to the analysis. Finally, a total of 4 studies were identified to be eligible for inclusion in the meta-analysis. All four studies underwent more detailed review. The detailed characteristics of the 4 included studies were shown in (Table 1).

6.2. Risk of Bias Evaluation

Based on the criteria set by Cochrane group, the quality of the studies was assessed independently by the two authors as seen in (Figure 2).

Three of the studies were deemed as having an unclear risk of bias given that patients were aware that they were being given midodrine versus human albumin. The intervention by itself is difficult to blind because the administration routes are different. However, this may not highly affect the results as the results are all laboratory-based.

6.3. Results of the Meta-Analyses: Efficacy Outcomes

6.3.1. Mortality: Mortality data were available in four of the randomized controlled trials, having a total sample size of 81 in the midodrine group and 83 in the albumin group. Nine deaths were reported in the midodrine group compared to 2 in the albumin group. Overall, there was no significant difference in the risk for mortality between the two groups, with an RR of 2.44 (95% CI 0.40-14.98, $p = 0.33$). Moderate heterogeneity was observed ($I^2 = 31\%$) among the four studies but was not statistically significant ($\chi^2 = 4.37$, $p = 0.22$).

6.3.2. PICD: Data for occurrence of paracentesis-induced circulatory dysfunction was available in only 2 studies. Six out of the 31 patients who were given midodrine after LVP developed PICD compared to 6 out of the 33 patients in the albumin group. There was no significant difference between the two groups (RR 0.95, 95% CI 0.14-6.56, $p = 0.96$). There was moderate heterogeneity ($I^2 = 46\%$) which was not statistically significant ($\chi^2 = 1.86$, $p = 0.17$).

Three studies also included baseline and post-treatment values for plasma renin (Appendrodt et al.) and plasma renin activity (Hamdy et al., Singh et al.). Standardized mean differences were computed and statistical analysis showed no significant difference in the change in PR/PRA between the two groups. Statistically significant heterogeneity however was observed among the studies in this analysis ($\chi^2 = 12.16$, $p = 0.002$, $I^2 = 84\%$).

6.3.3. Hyponatremia: Incidence of hyponatremia was assessed in all four included studies. A total of 3 out of 81 patients in the midodrine group met the pre-defined criteria for hyponatremia compared to 1 out of the 83 in the albumin group. Statistical significance was not met with a computed RR of 1.74 (95% CI 0.10-29.48, $p = 0.18$). Moderate heterogeneity was observed ($I^2 = 43\%$) but was not statistically significant ($\chi^2 = 1.77$, $p = 0.18$).

Post-treatment change in serum sodium levels were analyzed from the four studies and showed a trend that patients in the midodrine group had greater reduction in serum sodium compared to those

treated with albumin, with a mean difference of -1.61 mEqs/L (95% CI -3.51-0.28). Statistical significance, however, was not met (p = 0.10). Substantial heterogeneity was also observed in this analysis (χ^2 = 11.10, p = 0.01, I^2 = 73%).

6.3.4. Acute Kidney Injury: The criteria for assessing renal impairment were similar across the four studies. A total of 15 out of 81 patients in the midodrine group were observed to have AKI compared to only 6 out of 83 in the albumin group. Although there was a trend toward increased risk for AKI for midodrine with RR of 3.07 (95% CI 0.33-28.27), this did not meet statistical significance (p = 0.32). Heterogeneity was also noted to be substantial (I^2 = 66%) and statistically significant (χ^2 = 5.87, p = 0.05).

Analysis of the post-treatment changes in the serum creatinine levels showed no significant differences between the two groups, with a mean difference of 0.03 mg/dL (95% CI -0.20-0.25) in the midodrine group compared to albumin. Substantial heterogeneity which was statistically significant however was observed in this analysis (χ^2 = 15.19, p = 0.002, I^2 = 80%).

6.3.5: Quality of Evidence: (Table 2) shows a summary of the articles along with the quality of evidence.

7. Discussion

Many studies have been done in search for a suitable alternative to albumin for cirrhotic ascites. To the researchers' knowledge, the meta-analysis done was the first to primarily evaluate the effect of midodrine in terms of mortality and development of PICD in cirrhotic adult patients. This may be due to the small number of trials comparing midodrine and albumin.

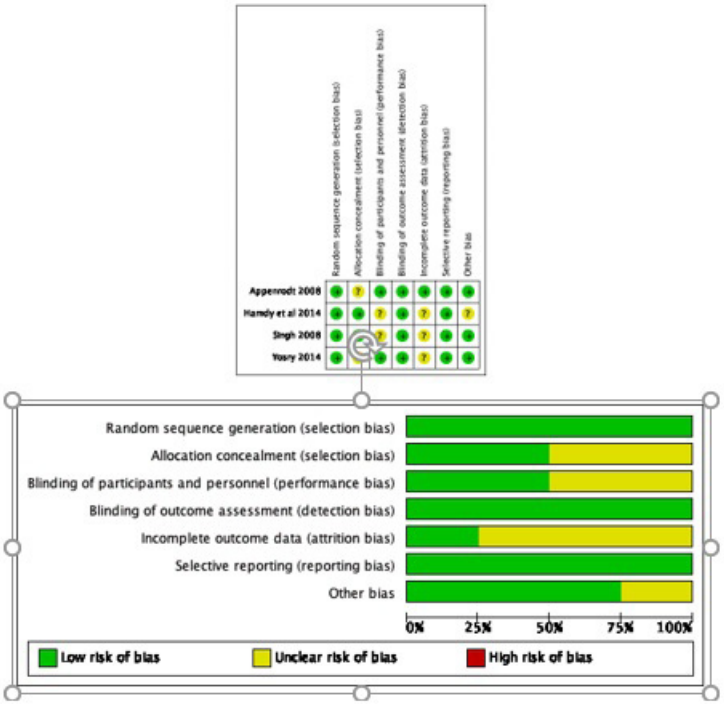

Figure 2: Risk of bias summary

Table 1: Characteristics of the studies included in the metaanalysis

	Author, Year	Study Design	Sample Size (n)	Population (Baseline Characteristics)	Intervention	Control	Outcome
1	Hamdy et al (2014)	Randomized control trial	50	Patients with cirrhosis, tense refractory ascites, less than 70 years of age and more than 18 years of age; absence of other disease, sepsis, SBP, encephalopathy, absence of recent use of diuretics, B blockers, plasma expanders or paracentesis	Total paracentesis done; Midodrine administered orally at 12.5mg every 8 hours for 3 days	Albumin dose of 8g/L of ascitic fluid removed	Midodrine in a fixed short term dose is not as effective in preventing circulatory dysfunction with increase in crea and development of hyponatremia in Midodrine group

2	Singh et al (2008)	Randomized control trial	40	Patients with cirrhosis, tense refractory ascites, less than 70 years of age; absence of other disease, sepsis, SBP, encephalopathy, absence of recent use of diuretics, B blockers, plasma expanders or paracentesis	Paracentesis done, Midodrine administered orally at 5-10mg every 8 hours to maintain MAP	Albumin dose of 8g/L of ascitic fluid removed giving within 2 hrs	the results of this study indicate that mido- drine may be as effective as albumin in the prevention of PICD in cirrhotics
3	Appenrodt et al (2008)	Randomized double blind control trial	24	Patients with cirrhosis, tense ascites, age < 70 but > 18; absence of coagulopathy/renal failure, SBP;absence of recent use of diuretic therapy/albumin	Paracentesis done, Midodrine given orally at 12.5mg every 8 hours for 2 days	Albumin dose of 8g/L of ascitic fluid removed after paracentesis	midodrine administered over 2 days is not as effective as albumin in the prevention of circulatory dysfunction
4	Yosry et al (2014)	Randomized control trial	75	Patient with cirrhosis, tense ascites, age > 70, less < 10, absence of sepsis, coagulopathy/renal failure, SBP, other diseases	Paracentesis done, 2 groups of Midodrine: 25 patients received 12.5 mg every 8 hours for 2 days; 25 patients received midodrine 12.5mg every 8 hrs for 30 days after LVP	Albumin dose of 8g/L of ascitic fluid removed after paracentesis	midodrine is non-inferior to albumin infusion in terms of maintaining renal functions, serum sodium, and 24 h urinary Na excretion in postviral hepa- titis cirrhotic patients with refractory ascites after LVP, and hence is comparable to albumin in preventing the effects of PICD

Table 2: Summary of Findings. RR: relative risk, MD: mean difference, SMD: standardized mean difference

Outcome	No of patients		Effect (95% CI)	Number of Individuals	Quality of the Evidence
	Midodrine	Albumin		(Number of Studies)	
Mortality	9/81 (11.1%)	2/83 (2.4%)	RR 2.44 (0.40 to 14.98)	164 individuals (4 studies)	⊕⊕⊕⊖ Moderate
PICD	6/31 (19.4%)	Jun-33 -18.20%	RR 0.95 (0.14 to 6.56)	64 individuals (2 studies)	⊕⊕⊖⊖ Low
Hyponatremia	Mar-81 -3.70%	Jan-83 -1.20%	RR 1.74 (0.10 to 29.48)	164 individuals (4 studies)	⊕⊕⊕⊖ Moderate
Acute Kidney Injury	15/81 -18.50%	Jun-83 -7.20%	RR 3.07 (0.33 to 28.27)	164 individuals (4 studies)	⊕⊕⊕⊖ Moderate

Plasma Renin / Plasma Renin Activity	56	58	SMD 0.33 (-0.64 to 1.29)	114 individuals (3 studies)	⊕⊖⊖⊖ Very Low
Serum Sodium	81	83	MD -1.61 mEq/L (-3.51 to 0.28)	164 individuals (4 studies)	⊕⊖⊖⊖ Very Low
Serum Creatinine	81	83	MD 0.03 mg/dL (-0.20 to 0.25)	164 individuals (4 studies)	⊕⊖⊖⊖ Very Low

In terms of all-cause mortality, analysis of the four included studies showed no significant difference between the two groups. Looking at the pooled raw data however would show a disparity between the groups - with 9 out of 81 deaths in the midodrine group compared to only 2 out of 83 in the albumin group. Among the four included studies, the one by Hamdy et al. evidently led to the divergence of the results, contributing 7 out of the 9 reported deaths in the midodrine group. In their study, they found out that 6 of these patients who died were cases of hepatocellular carcinoma (HCC). Furthermore, their subgroup analysis showed that in the midodrine group, HCC-positive individuals had significantly altered laboratory parameters (increased serum creatinine, decreased serum sodium, increased plasma renin activity) compared to HCC-negative patients, while analysis on the albumin group failed to show this trend. They hypothesized that midodrine might have low efficacy for HCC patients due to higher levels of nitric oxide or due to vascular hyporesponsiveness from a defective Rho-A/Rho-kinase signaling [15].

Data for occurrence of PICD, as per definition, was available in only 2 of the included studies. Although statistical analysis shows no significant difference in the occurrence of PICD in both groups, the different results of the two included studies makes it difficult to infer regarding the exact role of midodrine in the prevention of PICD. Another point to be considered is how assessing PICD biochemically through measurement of changes in plasma renin activity might not fully translate to clinical outcomes. For instance, the study by Yosry et al. assessed PICD through hemodynamic parameters including MAP, portal vein flow, and renal artery resistance indices.

Hyponatremia results as a consequence of circulatory dysfunction among patients with cirrhosis and is considered a predictor of adverse prognosis as it heralds occurrence of other complications of advanced liver disease such as hepatorenal syndrome and hepatic encephalopathy [20]. In this meta-analysis, occurrence of hyponatremia as per definition was comparable in both groups with an incidence of 3.7% in the midodrine compared to 1.2% in the albumin group. The slightly higher rate of hyponatremia in the midodrine group is consistent with the change-from-baseline analysis done (see Appendix) which showed that serum sodium levels did decrease in the midodrine group (mean change: -2.01 mEqs/L, 95% CI -3.12 to -0.91) compared to the equivocal results in the albumin group (mean change: -0.98 mEqs/L, 95% CI -3.46 to +1.98). Barring issues on precision of the data, such small decrease in serum sodium is unlikely to affect clinical decision to withhold treatment with midodrine.

Similar to the mortality analysis, data for occurrence of acute kidney injury was largely skewed by the results of the study of Hamdy et al. This led to a very imprecise estimate of the relative risk (95% CI 0.33 to 28.27). Excluding it from the analysis (see Appendix) however showed the same overall conclusion - no significant difference in the occurrence of AKI between the two groups - albeit with a smaller confidence interval.

8. Limitations

Most of the available studies on midodrine in comparison with human albumin are limited in terms of their small population, non-blinding, and heterogeneity with the dosage of midodrine. The very low to moderate quality of evidence for the primary or secondary endpoints, as assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group limited the ability of the study to conclude that there is a benefit in using midodrine**.** Larger, multi-centered and double-blinded randomized controlled trials are needed to have better data to support the efficacy of midodrine.

9. Conclusion

In conclusion, the meta-analysis focused on the efficacy of midodrine compared to albumin in decreasing mortality and PICD among cirrhotic ascites. The study showed that among the studies there seems to be no significant difference in terms of mortality and development of PICD between the use of midodrine and albumin, meaning its use as an alternative especially in a low-resource setting may be considered. Human albumin is costly and therefore not affordable in the long run for many cirrhotic patients. It is also given intravenously and therefore not feasible in a lot of outpatient centers. Given the limitations, it is still up to the practitioner whether they will use midodrine. With larger, multi-centered and more double-blinded RCTs, stronger evidence may be gathered to support midodrine as an alternative in an outpatient setting.

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