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EFFICACY OF MIDODRINE PLUS OCTREOTIDE IN HEPATORENAL SYNDROME: A META-ANALYSIS

Hiremath Sharanabasayyaswamy Basayyaswamy[1]*, Lokikere Srinivas Devendrappa[2], Madalageri Naveen Kumar[3]

[1]Department of Pharmacology, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India
[2]Assistant Professor, Department of Pharmacology, J.J.M. Medical College, Davangere, Karnataka, India
[3]Post Graduate, Department of Pharmacology, J.J.M. Medical College, Davangere, Karnataka, India

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***Corresponding author**
Dr. S.B. Hiremath, Assistant Professor, Department of Pharmacology, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India
E-mail: dr.sharan83@yahoo.com

ABSTRACT
Hepatorenal syndrome (HRS) is a type of renal failure occurring in patients with cirrhosis, ascites and liver failure. Among the pharmacological treatment available, terlipressin has been found to be most efficacious vasoconstrictor agent in improving renal function. Though terlipressin has significant HRS reversal benefits, it lacks long term mortality benefits. Evidences on mortality benefits and renal failure reversal efficacy of midodrine plus octreotide in HRS are insufficient and controversial. The primary and secondary objectives of the study were to analyze mortality benefits and HRS reversal efficacy of midodrine plus octreotide in HRS respectively. Electronic databases were searched for the relevant articles in PUBMED, The Cochrane Register for Controlled trials, SCIRUS and Google scholar with MeSH search terms'midodrine' 'octreotide' and 'hepatorenal syndrome'. Studies comparing mortality benefits of midodrine plus octreotide with control group were eligible to be included under analysis. Of the total 26 studies found relevant and deemed further screening only three studies met the eligibility criteria and were included in analysis. With total 309 patients included in analysis there was significant decrease in odds of occurrence of death at three months (Odds Ratio, OR = 0.17; 95% CI= 0.03 to 0.96) in midodrine plus octreotide treated group. Results of the study suggest that mortality benefits of midodrine plus octreotide appear to be significant even at three months. Though HRS reversal efficacy of this combination remains inconclusive, this combination may have HRS reversal benefits in terms of retarding the progression of the HRS rather than reversing it.
Key words: Midodrine, Octreotide, Hepatorenal syndrome

INTRODUCTION

As defined by international ascites club, Hepatorenal syndrome (HRS) is a potentially reversible syndrome occurring in patients with cirrhosis, ascites and liver failure.[1] HRS is a type of functional renal failure occurring in patients with cirrhosis of liver with an annual incidence of around 18%.[2] Based on the clinical features and prognosis it is classified into type 1 and type 2 HRS. Type 1 HRS is rapidly progressive with mean survival period of two weeks and one month mortality rate of around 95% if untreated. On the other hand, type 2 HRS is slowly progressing with better prognosis and mean survival period of six months[1-3]. Diagnosis of HRS is essentially based on the presence of five diagnostic criteria recently revised by International Ascites Club[1].

Targeting the basic pathophysiology of intense splanchnic vasodilatation and decreased systemic arterial pressure leading to decrease in effective blood volume and reduced renal perfusion, pharmacological treatment for reversing HRS has been mainly achieved by using various vasoconstrictor drugs along with plasma expander albumin.[1-3] Although liver transplantation is the treatment of choice in HRS, implication for reversing HRS by vasoconstrictor drugs in these patients is to improve renal function and transplant-free survival period which can serve as a bridge to liver transplantation in a greater number of patients. Improving renal function before liver transplantation is also associated with better post-transplantation mortality benefits.[4,5] Among the pharmacological treatment available, terlipressin has been found to be most efficacious vasoconstrictor agent in improving renal function.[6] Though terlipressin has significant HRS reversal benefits, it lacks long term mortality benefits.[6] Similarly, controversy remains over the efficacy of combination of alpha adrenergic agonist midodrine plus octreotide a somatostatin analogue in HRS with studies reporting significant mortality benefits[7-9] in presence of contradictory evidences on HRS reversal efficacy.[4,10-12]

To our knowledge there are no randomized controlled studies and meta-analyses reviews so for conducted on analyzing efficacy of the midodrine plus octreotide in HRS. With this background present meta-analysis was conducted with the aim to analyze mortality benefits and HRS reversal efficacy of midodrine plus octreotide using data from available observational studies.

MATERIALS AND METHODS

Eligibility criteria for studies to be included under meta-analysis

Studies comparing and publishing mortality benefits of midodrine plus octerotide versus control group were considered eligible for the analysis. Because of scarcity of studies on midodrine plus octreotide all types of studies irrespective of their study design were considered for analysis. Studies recruiting patients of HRS diagnosed as per the International Ascites Club framed criteria, of either sex aged above >18 years were eligible to be included under analysis.

Search strategy for identification of studies

Two co-authors independently conducted electronic data base search for the relevant articles in PUBMED, The Cochrane Register for Controlled trials, SCIRUS and Google scholar with MeSH search terms 'Midodrine'

'Octreotide' and 'Hepatorenal syndrome'. Manual search of bibliographies of all the relevant articles on midodrine plus octreotide was also carried out. Search was restricted to those studies published up to October 2011, either as full text or as abstract irrespective of language of publication. No additional search on conference proceedings and unpublished studies was done.

Data extraction

Relevant articles were identified and isolated by two co-authors. Further access into full publication details of these selected articles was then conducted for assessing their eligibility for inclusion under analysis. Published data and other study characteristics were extracted from studies meeting eligibility criteria. Published data independently extracted by two authors was considered for preparing final data after achieving consensus between two authors. For analyzing mortality benefits number of deaths at different time period and at the end of study period or maximum days of follow-up was extracted. For studies with incomplete published data, it was planned to request corresponding authors of individual studies for the required data through electronic mail.

Outcome measures

Difference in the mortality rate due to all causes of death was the primary outcome measure. Change in serum creatinine level was selected as secondary outcome measure as HRS reversal efficacy of vasoconstrictors is reported by most of studies by analyzing this parameter.

Statistical methods

Mortality benefits of midodrine plus octreotide against all causes of death was analyzed by calculating the Odds Ratio (OR) for occurrence of death as event in midodrine plus octreotide group (with or without albumin/other drugs) versus control group (with or without albumin/other drugs). We planned to analyze HRS reversal efficacy by calculating change in serum creatinine level as Mean Difference (MD) observed in serum creatinine level between two groups. All the outcome measures were analyzed by both DerSimonian and Laird random effects model and Mantel-Haenszel fixed effect model. Results of random effects model were considered for analysis and reporting of mortality benefits. A sub-group analysis of mortality benefits in patients with type 1 HRS was also conducted. Robustness of the results was assessed by comparing the results of random effect model with fixed effect model. Cochrane Q test for heterogeneity and I^2 test were used for analyzing inter-trial heterogeneity. A chi square test p value <0.10 and I^2 test value >50% were considered as an indicators of significant heterogeneity. RevMan software version 5.1.5 by Cochrane collaboration was used for statistical analysis.

Publication bias and quality evaluation

Though quality analysis in meta-analyses of observational studies is controversial, and even though all our eligible studies were not observational studies, as per the MOOSE criteria for reporting meta-analysis of observational studies structured review for quality evaluation as described by Nancy *et al*. was conducted.[13, 14] Un-blinded quality assessments of published data was independently performed by two authors and then a consensus was achieved on the final score after discussion between the authors. We planned to analyze publication bias by funnel plot method.

Table 1: Baseline demographic and clinical features of included studies

Study	Angeli *et.al*		Esrailian *et.al*		Skagen *et.al*	
Feature	**Treatment Group (n=5)**	**Control Group (n=8)**	**Treatment Group (n=60)**	**Control Group (n=21)**	**Treatment Group (n=75)**	**Control Group (n=87)**
Age [Years]	62 ± 3	61.3 ± 3	46.6	51.2	51±10.87	54.47±11.39
Gender [M&F]	N/A	N/A	N/A	N/A	50 & 25	52 & 35
Alcoholic Cirrhosis patients (%)	40%	37.5%	66.6%	52.3%	57.3%	51.7%
MAP (mm Hg)	75.9 ±3.0	78.9 ± 3.6	N/A	N/A	N/A	N/A
CP Score	N/A	N/A	11.4	10.8	N/A	N/A
MELD score	N/A	N/A	28.3	25.8	31.60±7.34	32.07±8.89
S.Bilirubin (mg/dl)	4.3± 1.3	6.1± 2.0	15.2	9.2	N/A	N/A
S.Creatinin (mg/dl)	5.0 ± 0.9	3.6 ±0.6	2.1±N/A	1.4±N/A	2.53±1.23	2.62±1.17

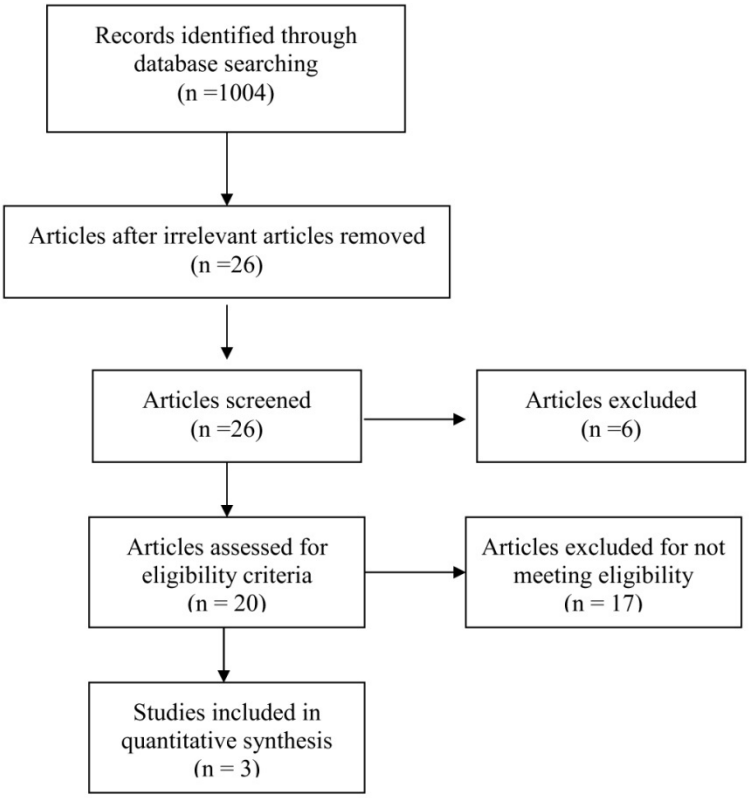
N/A: Not Available, CP Score: Child Pugh score, MAP: Mean Arterial Pressure, MELD Score: Model for End-Stage Liver Disease score, MOA: Midodrine, Octrotide and Albumin. Values in Mean ± Standard deviation

Table 2: Characteristics of included studies and interventions used

Study	Study design and country of origin	Duration of treatment (days)	Interventions	Quality score (% of maximum)
Skagen *et al*. (MOA Vs C)	Retrospective cohort (USA)	8.4±9.6 (mean ±SD)	M : 7.5-15mg mg TID, oral O : 100-200 µg TID,SC A : 50 to 100 g/d, IV	26/39 (66.6%)
Esrailian *et al*. (MO Vs C)	Retrospective Cohort (USA)	17 days (mean)	M : 5-15mg TID, oral O : 100-200 µg TID, SC	25/39 (64.10%)
Angeli *et al*. (MOA Vs D+A)	Non-randomized dopamine controlled (Italy)	20 days (maximum)	M : 7.5-12.5mg TID, oral O : 100-200 µg TID, SC A : 20-40g/d, IV D : 2-4 µg/kg/min, IV	20/39 51.28%

M: Midodrine; O: Octreotide, A: Albumin; D: Dopamine; C: control (treatment unclear); SC: subcutaneous; IV: intravenous

Fig.1. Flow chart showing study attrition diagram and number of trials included in meta-analysis.



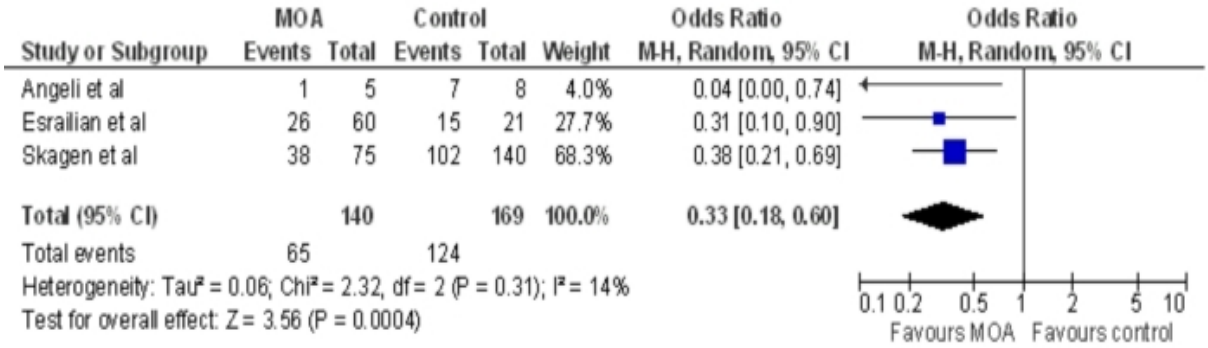


Figure 2: Forest plot showing the odds ratio for mortality benefits at the end of 1 month

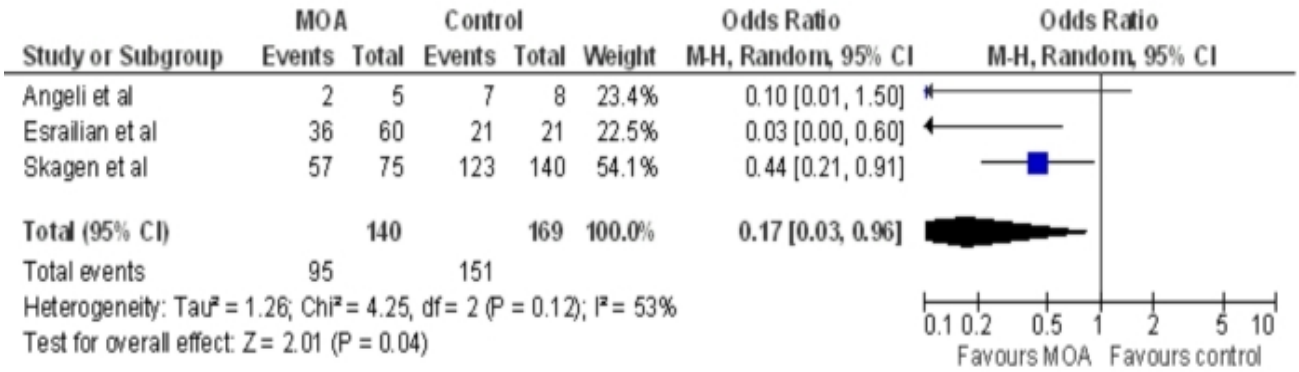


Figure 3: Forest plot showing the odds ratio for mortality benefits at the end of 3 month

RESULTS

Search results

Figure 1 shows study attrition diagram and number of studies included in analysis. We did not come across any eligible study published in literature other than English. Of the total 26 studies found relevant and deemed further screening, four were randomized controlled studies comparing either midodrine or cotreotide alone; one was cross-over study comparing midodrine with frusemide, three were retrospective cohort studies, two were prospective studies, seven were case series, two were case reports, one was case-control study, five were review articles and remaining one was letter to editor. Two retrospective cohort studies and one prospective study met eligibility criteria and were included under analysis.[4,10, 15]

Baseline characteristics of included studies

Baseline demographic and clinical features of the patients included in three eligible studies are as shown in Table 1. There were no statistically significant differences in the major baseline and clinical characteristics of midodrine plus octreotide group and control group in all three studies except for serum albumin level in study by Esrailian *et al*. and number of patients with asceits in study by Skagen *et al*. (not shown in table). Study by Skagen *et al*. is the largest study including total 162 patients followed by study by Esrailian *et al*. including 81 patients.[10,15] Possible influence on results due to small sample size from study by Angeli *et al*. which included only total 13 patients can be expected.[4] Unlike other two studies which included only patients of type 1 HRS, study by Skagen *et al*. included patients of both types of HRS. However, as the data on mortality benefits in patients with only type 1 HRS were available, data required for analysis of mortality benefits in type 1 HRS was also extracted from this study.

Interventions used and Follow up

As shown in Table 2, in all the eligible studies midodrine plus octreotide was used for mean duration of more than five days. Study by Esrailian *et al*. is the only exception among three studies where albumin was not used as an intervention in both groups. In addition, patients in both groups with alcoholic hepatitis as etiology of cirrhosis were administered pentoxifylline 400 mg daily orally. In study by Angeli *et al*. nonpressor doses of dopamine was used in control group against midodrine plus octerotide group. As the nonpressor doses were used, possibility of bias or influence of this intervention on outcome measures could be considered negligible and hence this group comparable to control groups of other two studies. Follow up data on mortality rate up to three months were available from all the three studies.

Results of outcome measure

As shown in Figure 2 and 3, with overall 309 patients analyzed there was a significant decrease in odds of occurrences of death in midodrine plus octreotide treated group at one month (Odds Ratio, OR = 0.33; 95% CI = 0.18 to 0.60) and three months (OR = 0.17; 95% CI = 0.03 to 0.96). There was no evidence for significant inter-trial heterogeneity with regard to one month mortality benefits (chi square p value = 0.31 and I^2 value of 14%) and results appeared to be robust on comparison with fixed effect model (OR = 0.34; 95% CI = 0.20 to 0.55). Although there was evidence for significant mortality benefits at three months, results were found not as robust as one month mortality rate when compared with fixed effect model (OR = 0.27; 95% CI = 0.14 to 0.51). In addition, there was evidence for possible inter-trial heterogeneity (chi square p value = 0.12 and I^2 value = 53%).

Interestingly, subgroup analysis of mortality benefits in type 1 HRS patients at both one month and three months was highly significant in midodrine plus octreotide group (figures not shown). With total 196 patients included, significant decrease in odds of occurrence of death at one month (OR = 0.26; 95% CI= 0.14 to 0.56) and three months (OR = 0.17; 95% CI= 0.03 to 0.83) were observed. In addition, there was no evidence for significant inter-trial heterogeneity with regard to mortality benefits at both one month (chi square p value 0.41 and I^2 value = 0%) and three months (chi square test p value = 0.18 and I^2 test value = 41%). Results appeared to be robust as odds ratio for occurrence of death at the end of both one month (OR = 0.26; 95% CI= 0.14 to 0.51) and three months (OR = 0.18; 95% CI= 0.07 to 0.46) by fixed effect model were also significant and similar to random effects model. Hence one month and three months mortality benefits of midodrine plus octreotide in type 1 HRS appear to be highly significant.

As data required for analyzing the change in serum creatinine level were available only from study by Angeli *et al*., we could not analyze effect size value for this parameter. Mean and standard deviation values for the change in serum creatinine level at the end of one month was not published in study by Skagen *et al*. There was no baseline and after treatment serum creatinine level data published in study by Esrailian *et al*. In addition, data on the change in serum creatinine level observed in study by Skagen *et al*. for patients with only type 1 HRS was also not available. Hence subgroup analysis of HRS reversal efficacy of this combination in type 1 HRS also could not be carried out. We did not received response for request on these data from the corresponding authors of these two studies. Hence we decided to summarize the observations of individual studies on HRS reversal efficacy. Similarly as the sufficient data required for safety analysis and efficacy of this combination on mean arterial pressure (MAP) were not available from eligible studies, we could not analyze the effect of this combination on these two important outcome measures.

Quality evaluation and publication bias

As all the studies were non-randomized studies, none of the included studies scored >70% of maximum possible score for un-blinded quality evaluation (Table 2). Study by Angeli *et al*. scored lowest possible score among the three studies. Possible influence of low quality evaluation score of included studies is a major limitation of our conclusion on the mortality benefits and HRS reversal efficacy of midodrine plus octreotide. As numbers of studies included in analysis were only three no publication bias assessment was carried out.

DISCUSSION

Results of our study reveal that combination of midodrine plus octrotide has significant mortality benefits in type 1 HRS both at one month and three months. However evidences for HRS reversal benefits of this combination could not be quantified with an effect size value due to insufficient data on change in serum creatinine level from two of the three eligible studies. Hence we summarize the HRS benefits of midodrine plus octreotide. Factors that significantly influence HRS reversal (decrease in serum creatinine level to ≤1.5mg/dl) efficacy of vasoconstrictors are amount of increase in MAP achieved and baseline severity of renal and hepatic failure.[16-18] Patients with baseline severe renal failure (serum creatinine level >5mg/dl), severe hepatic failure (Child Pugh score of >12) and those who fail to achieve required increase in MAP after treatment with vasoconstrictors have poor prognosis of achieving HRS reversal.[16-18] Severe renal failure may have significant and independent influence on the HRS reversal even after achieving sufficient increase in MAP owing to possible onset of functionally irreversible damage to the renal tubular cells.[4]

Differences in HRS reversal benefits observed in three eligible studies are addressed with regard to these influencing factors. Patients of both group in study by Esrailian *et al*. were at better prognostic side with regard to baseline severity of renal and hepatic failure (mean serum creatinine level <5mg/dl and Child Pugh score of <12). In addition, treatment group received midodrine plus octreotide in sufficient doses till an increase of at least 15mm Hg of MAP is achieved. With all the favorable factors study recorded fairly good results in terms of significant increase in HRS reversal rate although change in serum creatinine level in midodrine plus octreotide treated group was statistically nearly significant (p=0.06) even in absence of continued plasma expansion with albumin. Considering significant mortality benefits achieved results of the study support the view of positive correlation between HRS reversal benefits and mortality benefits observed with vasoconstrictors.[18, 19] The major discrepancy with regard to HRS reversal benefits and mortality benefits arise from study by Skagen *et al*. Study records significant mortality benefits in absence of HRS reversal benefits even after plasma expansion with sufficient dose of albumin. In absence of significant difference with regard to baseline severity of renal and hepatic failure between treatment groups and observed significant increase in Glomerular Filteration Rate (GFR) after treatment in midodrine plus octreotide group, failure to achieve HRS reversal even after achieving a significant increase in MAP in treatment group can perhaps be attributed to onset of functionally irreversible damage to tubules in major proportion of patients. Adding further to controversy is findings of study by Angeli *et al*. where in even though baseline severity of renal failure in treatment group is towards bad prognosis side (mean baseline serum creatinine level >5mg/dl), a significant increase in GFR along with significant HRS reversal benefits and mortality benefits were observed. Considering the positive correlation between duration of treatment with terlipressin and its HRS reversal efficacy, differences in HRS reversal benefits observed with midodrine plus octreotide between studies by Angeli *et al*. and Skagen *et al*. could be explained on the basis of differences in their duration of treatment (8.4±9.6 days in Skagen *et al*. vs 20 days in Angeli *et al*.).[20] In addition, considering the differences in sample size of treatment groups between these two studies (75 in Skagen *et al*. vs 5 in Angeli *et al*.), positive results from study by Angeli *et al*. seems expectable. Influence of variation in dose of albumin used (50-100 g/day in Skagen *et al* vs 20-40 g/day in Angeli *et al*), type of HRS patients included (both types in Skagen *et al*. vs only type 1 in Angeli *et al*) and endpoint day on which creatinine level reported (at 30 days in Skagen etal. vs 10 days in Angeli *et al*.) in these two studies also needs to be considered. However consistent with both studies is finding of significant improvement in GFR and renal perfusion by midodrine plus octreotide.

Rationale behind combination of midodrine an alpha adrenergic agonist and octreotide a somatostatin analogue is the synergism of vasoconstrictor effect of midodrine and inhibitory effect of octreotide on release of endogenous vasodilators responsible for hemodynamic alteration in HRS.[4] Arterial non-reactivity to vasoconstrictors is a poor prognostic factor responsible for failure to achieve significant increase in MAP and thus the non-responder state to vasoconstrictors.[16,17] Adding octreotide to vasoconstrictor midodrine should also addresses the issue of non-responder state to vasoconstrictors owing to its theoretical benefit of reversing arterial non-reactivity.[4] From this point of view midrodrine plus otreotide should have demonstrated better beneficial effects in terms of HRS reversal efficacy. Reason for failure could be because vasoconstrictor effects of midodrine mediated through alpha adrenergic receptors may not be as strong as to that of vasopressin analogues.[8] In addition it is opined that this combination may not achieve significant increase in MAP from baseline level and the correlation between amount of increase in MAP achieved and decrease in serum creatinine levels observed with midodrine plus octreotide also may not be as strong as vasopressin analogues.[16] However, as opined by authors of all three eligible studies an effective increase in MAP by at least 15mm Hg was successfully achieved in midodrine plus octreotide group at maximum dose of 15mg TID. In view of these contradictory opinions and observation of significant increase in renal perfusion observed in midodrine plus octreotide groups of two eligible studies, opinion that this combination may succeed in maintaining optimum renal perfusion enough to prevent progression of HRS not to reverse it seems reasonably acceptable.[12] Retarding the progression of HRS might be sufficient enough to prevent HRS related causes of death and hence mortality benefits against HRS as cause of death by midodrine plus octreotide in absence of HRS reversal efficacy. This hypothesis is supported by available data on individual causes of death in midodrine plus octreotide treated patients wherein HRS never constituted as a major cause of death.[4, 12]

It is opined that the selection of a vasoconstrictor drug in HRS which can effectively increase MAP from baseline by >10-15mm Hg should be based on their safety

profile.[16] Although there are no randomized studies comparing safety and efficacy of terlipressin with midodrine plus octreotide, considering the high rates of ischemic complications with terlipressin and evidences on relatively similar benefits of midodrine plus octreotide with terlipressin from an observational study, this combination could prove as better alternative to terlipressin.[7,15] However randomized blinded studies with adequate sample size would give conclusive evidence on this issue.

Strength of this study is analysis of three month mortality benefits in patients with type 1 HRS. All the included studies reported long term mortality rates up to end of three months so that long-term three month mortality benefits with midodrine plus octreotide in type 1 HRS appears to be highly significant. However none of the eligible studies are randomized studies is a major limitation to our conclusion on mortality benefits. Restriction to published studies and possibility of inter-trial heterogeneity with regard to duration of treatment and use of albumin are other limitations. In addition the numbers of studies included in analysis are less and the sample size may not be adequate enough to make such strong conclusions on mortality benefits. Majority of our opinions are based on evidences from uncontrolled observational studies or studies on terlipressin is also another limiting factor. In view of these limitations and limited availability of data, study findings of a meta-analysis may not be reasonable and hence need to be interpreted cautiously. Though our study failed to address the issue of HRS reversal efficacy of this combination, our study strongly supports possible long term mortality benefits associated with this combination and need for randomized studies to correlate its mortality benefits and HRS reversal efficacy.

CONCLUSION

Mortality benefits of midodrine plus octreotide appear to be significant even at three months. However though its HRS reversal efficacy is inconclusive, this combination may have HRS reversal benefits in terms of retarding the progression of the HRS rather than reversing it.

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