Systemic reviews and meta-analysis of the use of Midodrine in hepatorenal syndrome (HRS)

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ABSTRACT

Aims: This study aims to analyse how midodrine can reduce or manage Hepatorenal syndrome (HRS).

Design: This study created a systematic review and meta-analysis to address research goals and issues. It helps find relevant information in articles and literature. Targets and goals determine keywords and search criteria in this systematic review. Systematic reviews assess study aims, backgrounds, and goals. This systematic review reviews the selected studies' methodologies, outcomes, and effects. Key findings from chosen studies are highlighted in this review. The tabular analysis makes data more accessible to see. The study used a systematic review design to find data and generate a report swiftly.

The design covers authors, research goals, methodologies, findings, and implications. Data gathering and analysis are systematic review tasks. This method starts with an evidence-gathering query. The protocol specifies the search method, research selection criteria, and data extraction and analysis for transparency.

Data sources: The study then searches Google Scholar and PubMed for reputable articles. Using inclusion and exclusion criteria, a study is determined. Quality assessment data is extracted, synthesized, analyzed, and reported.

Review methods: A secondary search for systematic review retrieves relevant information from peer-reviewed journals, which has pros and cons. This improves report relevance, and analyzing aims, methods, and outcomes helps researchers understand their implications. This helps identify relevant data to accomplish study goals and answer queries. When choosing a strategy, this procedure considers time, language, and full-length article availability. Sometimes, this method excludes papers due to duplicity, abstract availability, non-English language, and other reasons.

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Result: The findings show how midodrine can enhance HRS patients' lifestyle and renal and liver problems. In both groups, arterial pressure increased significantly as renal function improved, showing a clear link between circulatory and renal function in patients. Terlipressin may improve renal function better than midodrine and octreotide because it affects mean artery pressure (MAP).
Conclusion: This study comprehensively evaluates midodrine in hepatorenal syndrome. Midodrine decreased nitrite and nitrate in ascites patients regardless of hepatorenal syndrome. Many studies have explored midodrine's hepatorenal syndrome treatment. The drug's efficacy and safety were studied in small groups. Significant, well-designed clinical trials are needed to address this issue. Few studies have indicated an ideal dosage or duration. Pharmacological side effects must be examined.
Impact: The meta-analysis opens various opportunities for midodrine research in hepatorenal syndrome. In combination treatment studies, midodrine can be given with octreotide or albumin. The study can also evaluate drug cost-effectiveness.
Keywords: Midodrine, Hepatorenal syndrome (HRS), treatment, medication, liver, diet, transplantation, blood pressure, renal condition, blood flow, renal failure, kidney failure

INTRODUCTION

Hepatorenal syndrome is a complex and severe liver illness characterized by a rapid deterioration in kidney function caused by disturbed blood circulation and flow. Furthermore, this syndrome induces renal vasoconstriction, resulting in renal failure caused by reduced renal blood flow. Midodrine is a medication that doctors give to treat orthostatic hypotension, a disease characterized by fainting and dizziness caused by low blood pressure. The rationale for performing systematic reviews and meta-analyses on the use of midodrine in hepatorenal syndrome is to evaluate this treatment approach's effectiveness and safety comprehensively. Therefore, through systematic reviews and meta-analyses, the available information from multiple studies may be combined to provide a more thorough understanding of the pros and cons associated with using midodrine in HRS (Hepatorenal syndrome). This data can offer direction for therapeutic decision-making and influence future research paths related to the care of this intricate ailment [1].

“Arterial vasodilation theory” is a conceptual framework within cardiovascular physiology and pharmacology that explains the role of dilation in various physiological and pathological conditions. This postulate describes the impact of activation of the vasoconstrictor system in maintaining the sodium level and free water. This theory explains alterations in arterial tone, mediated by endothelial function, neural regulation, and hormonal influences, can significantly impact cardiovascular health.

“Circular dysfunction” is another theory for liver cirrhosis and significant alteration in circulatory dynamics. The application of this theory assists in managing portal hypertension, increasing intra-abdominal pressure, and reducing cardiac output [2]. This contributes to impaired renal flow of blood and hypoperfusion. The “Circular dysfunction” theory emphasizes the connections and influencers of the disease. It highlights how conflicts, tensions, or unresolved issues among family

members or group members can escalate or persist due to feedback loops, where one person's behavior triggers a reaction in another, reinforcing the original behavior.

Mediodrine is typically an adjunctive therapy for hepatorenal syndrome; this is treated differently for this syndrome than orthostatic hypotension. For this reason, the analysis of the use of midodrine in hepatorenal syndrome is required to fetch valuable insight into both the syndrome and the midodrine medication system for its recovery. Midodrine is a vasoconstrictor that constricts blood vessels, thereby increasing blood pressure and improving circulation. This medication has few side effects, such as hypertension, urinary retention, and tangling in the scalp. To mitigate these risks, Midodrine is usually prescribed during the daytime.

Hepatorenal syndrome is a threatening liver condition that can be fatal to human health. No medication is proven to be adequate for this health issue. Some treatments can only prolong a person's life; however, less than 50% of patients can live after medication [3]. Hence, transplantation of the liver is the only proper treatment for the complete recovery of this disease. After the identification of this health issue, patients need to continue with a highly restricted diet, along with proper medication. In this concern, the risks and severity of this syndrome are managed. Hence, people must maintain a healthy type and regular treatment or healthcare for a healthy liver condition.

In liver cirrhosis, Portal hypertension mediates splanchnic arterial vasodilation, thereby initiating a decline in the vascular resistance of systemic vessels and resulting in adequate blood volume circulation. This phenomenon triggers several compensatory mechanisms, such as enhanced cardiac output by activating the sympathetic nervous system and renin-angiotensin-aldosterone [4]. As an outcome of these events, renal arteries drive the constriction of circulatory blood vessels, thus promoting a reduction in blood uptake by the kidneys. Impaired liver synthetic function drives sodium and water retention, and it is often attributed to hypoalbuminemia [5]. These can be cumulatively presented as edema and ascites clinically. The adverse effects of these conditions often show a higher propensity to develop acute kidney injury (AKI) and hepatorenal syndrome (HRS). The prevalence of HRS is exhibited in individuals with cirrhosis, and its vulnerability increases with prolonged exposure and the severity of the condition. A prospective study showed that HRS was exhibited in 18% of cases per year, and it experienced a significant spike to 39% after a period of 5-year follow-up [6]. Another study documented that approximately 48% of affected individuals awaiting liver transplantation (LT) were severely exposed to HRS. HRS drives an increased treatment cost and imposes socio-economic burdens despite its fatal effect on patient survival and effective outcomes. A retrospective analysis that involved 2542 hospitalized patients with HRS showed the average hospital stay per patient was approximately 30.5 days, with an average cost of $91,504 per admitted person [7].

BACKGROUND AND AIMS

HRS is a severe disease of the liver, leading to a lack of proper function of the kidneys and harmful changes in blood circulation. This results in ultimate renal failure due to reduced flow of blood in the kidneys. Midodrine is a medication procedure that is used to manage HRS issues. This aims at

managing blood vessels, especially the peripheral vascular beds, and the help of midodrine to increase blood pressure [8]. This assists in improving renal perfusion and functions. Adjunctive therapy and live transplant evaluation are some other treatment processes for HRS. This study aims to analyse how midodrine can reduce or manage Hepatorenal syndrome (HRS). The study hypothesizes that Midodrine can assist in the treatment and reduction of the negative effect of Hepatorenal syndrome (HRS).

DESIGN

This study is associated with the development of systematic review and meta-analysis, which focuses on research objectives and questions. This strategy is beneficial for finding relevant information from existing articles and literature. This systematic review design focuses on aims and objectives to develop keywords and maintain the search criteria. Furthermore, a systematic review assesses those studies' aims, objectives, and backgrounds [9]. It also analyses the method that the researchers of the selected studies have used; finally, this systematic review assesses the results, findings, and implications of those studies. In this way, this review process highlights the core information fetched from the selected studies. In addition, this analysis's tabular presentation increases the overall data's visibility. For this reason, this study selected this systematic review design to find the data quickly and construct a systematic report.

This design includes authors' names, research aims, methods, findings, and implications. The systematic review design is associated with the development of data collection and systematic analysis process. This process, at first, formulates a research question to find relevant evidence. Then, it sets the protocol outline search strategy, study selection criteria, and data extraction and analysis method to ensure transparency [10]. Next, it conducted a literature search from different databases; this study searched for information from Google Scholar and PubMed for various authentic journals. After that, the study is selected based on inclusion and exclusion criteria. After this, data is extracted for quality assessment, followed by data synthesis interpretation and reporting.

SEARCH METHODS

A secondary search for systematic review has positive and negative effects; this process systematically fetches relevant information from peer-reviewed journals. This increases report relevance; furthermore, analysis of aims and methods, along with results, assists the researchers in finding the implication of those research processes. This assists in finding relevant information to meet research objectives and answer the research questions [11]. In order to select a particular strategy, this process develops choices, such as time, language, and availability of full-length articles. Sometimes, this process rejects articles due to duplicity, the availability of only abstracts, the fact that the article's language is not English, and many other reasons.

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Inclusion and exclusion criteria

Criteria	*Inclusion*	*Exclusion*
Databases searched	Medical databases, such as PubMed	Other than medical databases
Languages	English only	Other than English
Time of the literature searched	2000 to 2024	Prior to 2000
Keywords	Midodrine, Hepatorenal syndrome (HRS), treatment, medication, liver, diet, transplantation, blood pressure, renal condition, blood flow, renal failure, kidney failure	Other than these

Table I: Inclusion and exclusion criteria

SEARCH OUTCOME

Applying inclusion and exclusion criteria is beneficial for extracting relevant data to develop a relevant search strategy. This criterion is a guidance or boundary to fetch the relevant or current data.

References are selected based on the source journals; apart from that, the peer-reviewed articles are only selected. Hence, this is associated with developing a systematic search and collection of data. The above inclusion and exclusion criteria are used for the overall strategy and to enhance efficiency in data collection.

Study	Summary
Cavallin et al., 2015	Hepatorenal syndrome (HRS) is a severe complexity of the liver system which increases the mortality rate without proper medication. Terlipressin is beneficial for HRS; the comparative analysis of HRS patients is based on two types of medication: Terlipressin and midodrine. This study revealed that the patient group with Terlipressin improved faster; their renal system was improved. It decided that Terlipressin plus albumin is more effective than midodrine and octreotide plus albumin for HRS patients.
Wong et al., 2004	Hepatorenal syndrome (HRS) is a renal disorder that increases bodily complexities through liver and kidney failure, leading to death. This study analyses the effectiveness of transjugular intrahepatic portosystemic stent shunt (TIPS) for HRS patients. This study concluded that TIPS is suitable for patients with cirrhosis and ascites. This also improves renal function, combining TIPS with octreotide, albumin, and midodrine.

Table II: Summarisation of included studies

Quality appraisal

PRISMA chart presents step-by-step data collection processes; in the first step, it gathers data from selected databases. This study gathered data from PubMed, MedlinePlus, and Web of Science. At this stage, duplicate records are removed. Then. Those articles were filtered in the screening test, and selected articles were deselected based on language, availability of complete articles, country concerns, and many other reasons. The last stage, "included," presented the final number of selected articles in a study. This study selected 15 articles at the final stage. PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is a guideline developed to improve the transparency and quality of reporting in systematic reviews and meta-analyses.

PRISMA primarily focuses on reporting guidelines (Slagboom et al., 2023). However, it indirectly supports quality appraisal by promoting comprehensive reporting of study methods, results, and conclusions. PRISMA provides a reliable, standardized structure of reviews and analyses in the context of quality appraisal.

The PRISMA-based review process has limitations in focusing on reporting action rather than conducting procedures, limited applicability, more focus on transparency than quality assessment, and lack of tailoring [12]. In some cases, PRISMA needs more specificity in the analysis as it provides general recommendations for the report. The guidelines of PRISMA cover limited regions by addressing reporting standards of meta-analysis and reviews.

This study used the Medical Subject Headings (MeSH) approach to assess the credibility of the research process and conduct a meta-analysis. The "Medical Subject Headings (MeSH)" study will include a systematic review that significantly impacts the review's credibility. MeSH terms, standardized vocabulary for indexing biomedical literature, improved search strategies, enhancing comprehensiveness and specificity [13]. Precision is enhanced by accurately identifying relevant studies, ensuring only high-quality ones are included.

DATA ABSTRACTION

In the systematic review process, the data abstraction focuses on developing research aims and objectives to enhance reliability. Then, this process looks into resolving discrepancies by analyzing the research method and participants included. Furthermore, data verification is conducted to check the availability of full-length articles.

SYNTHESIS

Gathered data is synthesized in several steps; at first, the summary of the overall process is assessed. The articles are gathered based on the research aim and objectives; in order to synthesize the information, this study presented information in tabular form. The headings in the table are the authors' names, aims, methods, findings, and implications.

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RESULT

Flow diagram of PRISMA

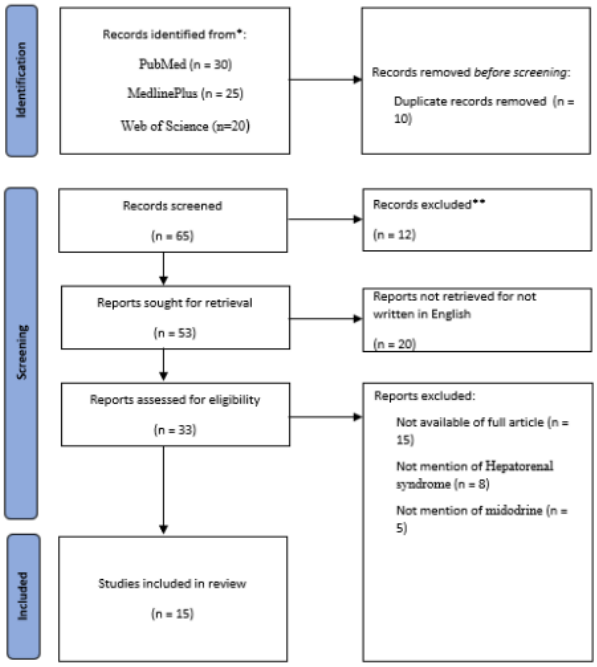

Fig. 1: PRISMA flowchart

Name of authors	*Aims*	*Method*	*Findings*	*Implication*
Cavallin et al., 2015	Finding better effectiveness of treatment processes between Terlipressin plus albumin and midodrine and octreotide plus albumin by analyzing responses of HRS patients	Comparative analysis based on treatment procedure: Terlipressin plus albumin and midodrine and octreotide plus albumin	Terlipressin plus albumin is more effective than the other	Terlipressin plus albumin will be used and is preferable for HRS patients
Wong et al., 2004	Determining the efficacy of transjugular intrahepatic portosystemic stent shunt (TIPS) as a treatment for type 1 HRS in ascitic cirrhotic patients	Comparative analysis of patients before and after the use of TIPS medical care	TIPS, suitable for patients with cirrhosis and ascites, improves renal function when TIPS is combined with octreotide, albumin, and midodrine	Midodrine can be used to increase the efficiency of TIPS treatment
Nanda, et al., 2018	Comparing the efficacy of various drugs in the treatment of HRS	The randomised controlled trial compares a placebo with two drugs. Secondary outcomes were performed on HRS patients	Subgroup analysis and controlled trials revealed that Terlipressin is more beneficial than placebo.	Terlipressin can be used to treat HRS patients.

Table III: Systematic analysis

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Descriptives

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation	Variance
Age	15	1	2	1.40	.507	.257
Effect of midodrine	15	1	2	1.20	.414	.171
Chances of cure HRS after drug application	15	1	2	1.13	.352	.124
Valid N (listwise)	15					

Table IV: Descriptive Statistics

From the descriptive statistics analysis it is seen that all variables are scale all the variables are between 48 to 55 years of age. Here, the total number of sample patients are 15. The standard deviation of age is 0.507 and variance is 0.257 which show low distribution of ages centring the mean age. Value of standard deviation and variance in effect of midodrine are 0.414 and 0.171 which suggest observable variability among the samples. Possibility of getting cured after the application of the drug shows variance of 0.124 and standard deviation of 0.352 that suggest a moderate level of variability.

Frequencies

Statistics

		Age	Effect of midodrine	Chances of cure HRS after drug application
N	Valid	15	15	15
	Missing	0	0	0
Mean		1.40	1.20	1.13
Std. Error of Mean		.131	.107	.091
Median		1.00	1.00	1.00
Mode		1	1	1
Std. Deviation		.507	.414	.352
Variance		.257	.171	.124
Skewness		.455	1.672	2.405
Std. Error of Skewness		.580	.580	.580
Kurtosis		-2.094	.897	4.349
Std. Error of Kurtosis		1.121	1.121	1.121
Range		1	1	1
Minimum		1	1	1
Maximum		2	2	2
Sum		21	18	17

Table V: Statistics

From the above frequency table, it can be concluded that, the skewness of the age is 0.455 which is positive and it suggest that there must be high number of older people among the samples. In case of midodrine's effect the skewness is positive also which is 1.672 indicating that there are high effects of the drug across the individuals. The skewness in the after effect of the drug application shows right skew and the value is 2.405 that indicates higher rates of cure of HRS. Kurtosis value of age is -2.094 and this negative value indicates that the distribution id platykurtic. The effects and result of the drug application have kurtosis are 0.897 and 4.349 respectively that indicates normal distribution but have slightly higher heavier tails and potentiality.

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Frequency Table

Age					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	48-51	9	60.0	60.0	60.0
	52-55	6	40.0	40.0	100.0
	Total	15	100.0	100.0	

Table VI: Frequency Table of Age

Among the 15 samples 9 participants fall under 48-51 years of age group that are 60% and 6 are from 52-55 years age group that shows it indicates 40% of the total sample.

Effect of midodrine					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	positive	12	80.0	80.0	80.0
	less effective	3	20.0	20.0	100.0
	Total	15	100.0	100.0	

Table VII: Frequency Table of Effect of midodrine

Frequency table of effect of midodrine suggests that the majority that is 80% of the participants exhibits positive effect and 20% are less effective.

Chances of cure HRS after drug application					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	high	13	86.7	86.7	86.7
	low	2	13.3	13.3	100.0
	Total	15	100.0	100.0	

Table VIII: Frequency Table of Chances of cure HRS after drug application

From the Frequency table of cure of HRS after the application of drug suggests that about 86.7% patients show high rate of recovery where as 13.3% exhibit low chances.

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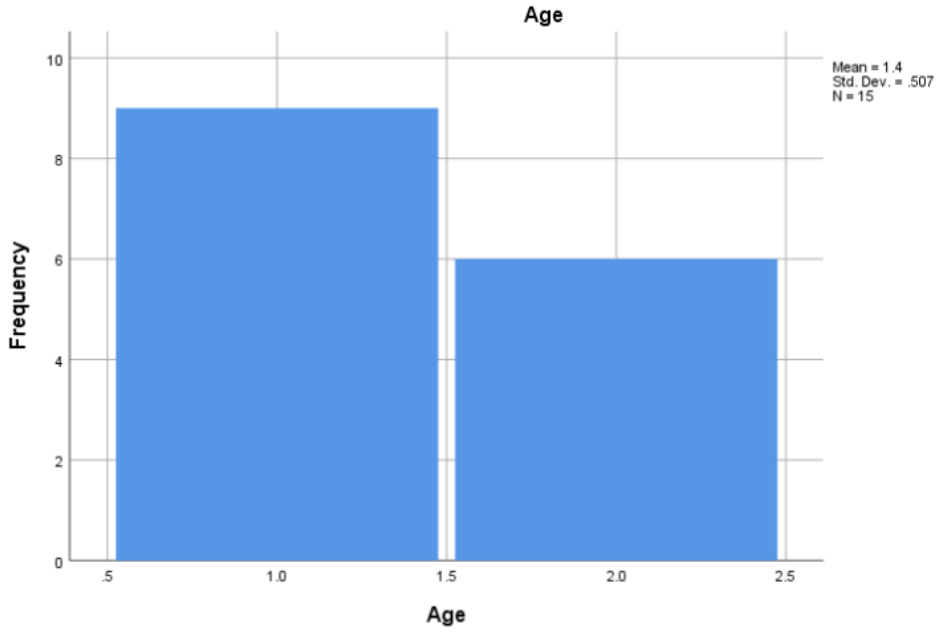
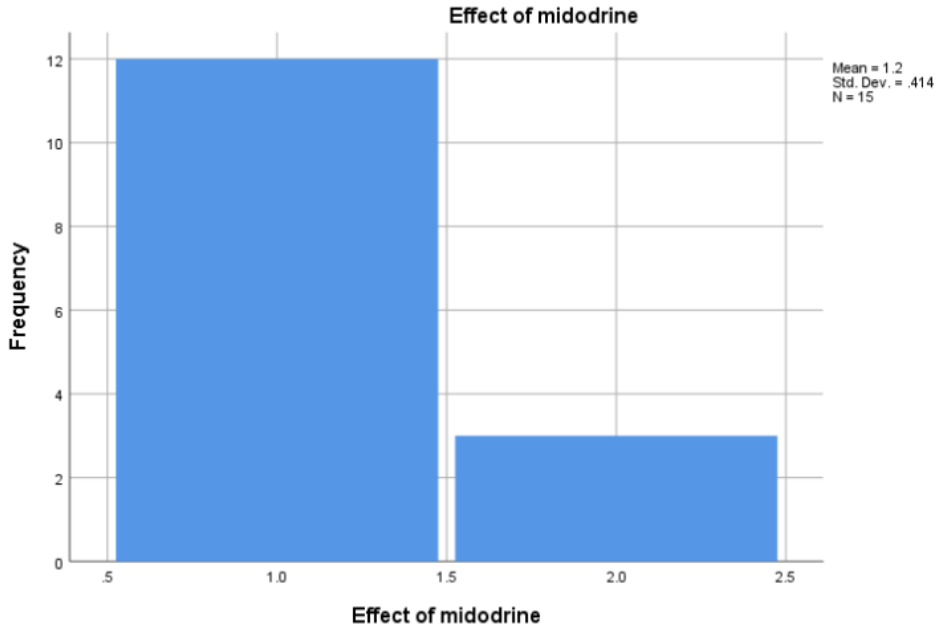
Histogram





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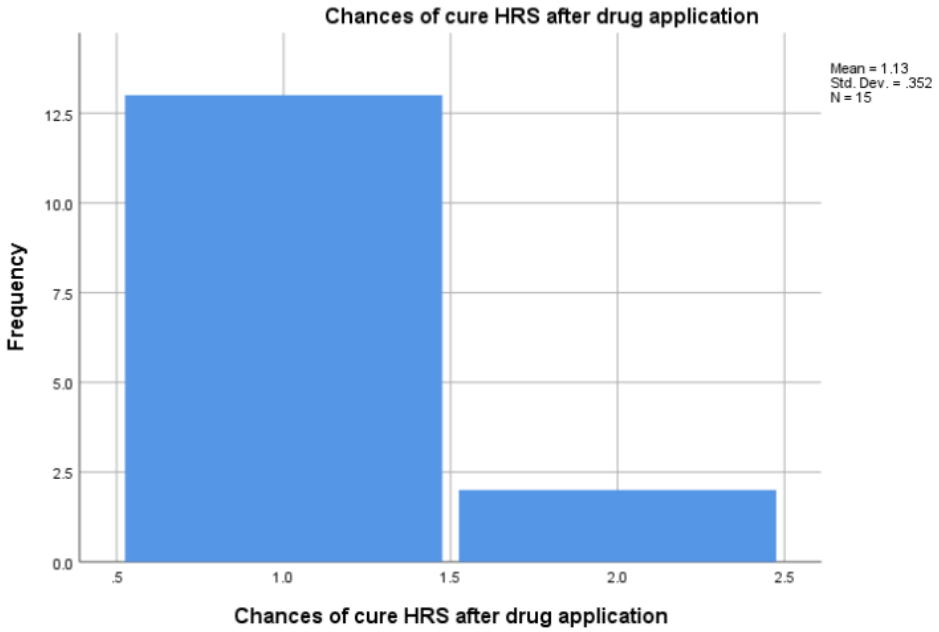

DISCUSSION

The findings highlight the way midodrine can be applied to HRS patients to improve their living and kidney and liver conditions. There was a significant correlation between the improvement in renal function and the increase in arterial pressure in people, suggesting a strong connection between circulatory and renal function in patients. The more significant influence of Terlipressin on mean arterial pressure (MAP) may account for its superior efficacy compared to midodrine and octreotide in enhancing renal function [14]. The observed renal response rate to midodrine, which stands at 28.6%, is within the anticipated range based on practical experience.

The use of midodrine and a vasoconstrictor in pharmacological therapy is extremely important as it acts as a temporary solution before liver transplantation. This is particularly crucial due to the high risk of short-term mortality associated with hepatorenal syndrome (HRS) and the limited availability of liver grafts. However, it is important to note that liver transplantation is the most effective and conclusive treatment for hepatorenal syndrome (HRS). Research has shown that the use of vasoconstrictors in the management of hepatorenal syndrome (HRS) can enhance survival rates. Furthermore, there seems to be a connection between the increase in mean arterial pressure induced by vasoconstrictors and the improvement in blood creatinine levels. Terlipressin, noradrenaline, or midodrine (when used with octreotide) are the recommended vasoconstrictor drugs for treating hemodynamically refractory syndrome. In order to maximize the effectiveness of these drugs, it is recommended to administer them along with albumin. Studies have been undertaken on terlipressin for the treatment of sepsis-related hepatorenal syndrome (HRS), and these studies found that 67% of patients experienced an improvement in renal function. Within a same framework, a retrospective analysis of the REVERSE experiment revealed that patients with

hepatorenal syndrome (HRS) accompanied by systemic inflammatory response syndrome (SIRS) exhibited a more robust reaction to midodrine compared to those with HRS but without SIRS. This was determined by contrasting patients diagnosed with hepatorenal syndrome (HRS) with those diagnosed with systemic inflammatory response syndrome (SIRS). According to these findings, midodrine may provide greater benefits for patients who are in a more critical condition, especially those who have a more pronounced inflammatory response and a greater influence on their hemodynamics. The standard treatment for hepatorenal syndrome (HRS) using midodrine involves giving intravenous boluses of 0.5-1.0 mg every 4-6 hours. The dose is then increased every two days, doubling the amount, until a maximum of 12 mg per day is reached. This treatment is administered if the patient's creatinine level does not decrease by more than 25 percent. Treatment can be prolonged for up to two weeks, however it may be stopped sooner if there is a full reversal of HRS. If HRS reoccurs, patients will be managed in a similar fashion. However, in recent times, there has been an increasing need to administer terlipressin through continuous intravenous infusion to reduce the occurrence of side effects.

Nevertheless, the response rate was lower than that of a previous, more extensive retrospective study (40%). In order to clarify the inconsistency, it is essential to note that the latter study utilized plasma volume expansion with saline alone and included 36% of patients with alcoholic hepatitis. On the other hand, the group treated with Terlipressin with albumin exhibited a notably more significant percentage of partial or complete renal responses (56% compared to 33.9%-39%) [15]. The percentages of complete and partial responses are 70% and 43.5%, respectively, for the ages 15 and 17. The difference in response to Terlipressin and albumin may be attributed to two variables. A pharmacodynamic study on individuals with cirrhosis revealed that midodrine exhibited a transient impact on portal pressure, lasting less than four hours. midodrine was administered as a continuous intravenous infusion in the ongoing experiment. Furthermore, according to the diagnostic recommendations established by the 2007 International Club of Ascites, individuals who have renal insufficiency and are currently experiencing bacterial infections are categorized as having Hepatorenal Syndrome (HRS). Recent research has shown that terlipressin and albumin treatment has resulted in a 67% success rate in persons with infection-related hepatorenal syndrome (HRS) [16].

This study shows type 1 HRS may be reversible functional renal disease. Intravenous albumin, octreotide, and midodrine improved renal function in type 1 HRS patients but did not restore normality. With the gradual elimination of ascites, TIPS can restore renal function in suitable patients after medicinal therapy. This investigation was conducted because Terlipressin, a vasoconstrictor routinely used in Europe for cirrhotic patients with type 1 HRS, was unavailable. A larger sample of type 1 HRS patients shows that the combination medication improves renal function in two-thirds using a similar methodology [17]. Combination therapy reduced vascular capacitance by combining midodrine's adrenergic agonist activity and octreotide's vasodilation inhibitory effect while replenishing intravascular volume with albumin. These findings align with type 1 HRS patients who received Terlipressin, resulting in a 64% reduction in serum creatinine levels from 272 ± 114 to 138 ± 59 mol/L.5 Thus, midodrine, octreotide, and albumin may treat

type 1 HRS in North America. Patients who responded to octreotide, midodrine, and albumin appear to follow the "peripheral arterial vasodilation hypothesis [18]." Cirrhosis-related renal impairment is caused by kidney vasoconstriction caused by systemic arterial vasodilation, arterial underfilling, and various vasoconstrictor systems. Thus, increased natriuresis reduced plasma renin and aldosterone and improved renal function by reducing arterial vasodilation and increasing intravascular volume. However, albumin, octreotide, and midodrine somewhat improved renal plasma flow, glomerular filtration rate, and salt excretion. No extra sodium excretion or renal hemodynamic improvements were observed with continuing dosing of these drugs. Despite treatment to reduce the discrepancy between intravascular and arterial vasodilation, nonresponders maintained elevated levels of multiple hormonal markers associated with vascular filling and continued declining renal function. Midodrine and octreotide may have caused "refractory" vasoconstriction in nonresponders. Cirrhosis is known for vascular nonresponsiveness (25–27). This may be due to a peripheral vascular malfunction or nitric oxide overproduction. Thus, the nonresponders may have had higher arterial vasodilation than the responders, resulting in lower concentrations despite the measured hemodynamic characteristics. Plasma renin, aldosterone, and norepinephrine levels were higher in nonresponders, suggesting greater arterial underfilling caused more hemodynamic disruption [19]. The most effective pharmacological intervention for reversing hepatorenal syndrome (HRS) is the intravenous infusion of Terlipressin. A viable option is the intravenous infusion of noradrenaline. Conducting research is necessary to establish a basis for creating pharmaceutical treatments that will enhance patient survival and reduce the likelihood of HRS recurrence.

A comprehensive literature review encompassed database and manual searches using reference lists, recommendations, and previously conducted meta-analyses. Two distinct data extraction procedures were conducted, and discrepancies were resolved through dialogue. The extra material contains a compilation of the research that was included. The essential attributes of the included studies are provided exclusively in the supplementary material for each study, without any summarization [20]. Various methodologies, such as network meta-analyses conducted within a Bayesian framework, combine the findings of multiple investigations.

The articles used for the meta-analysis tended to report just specific outcomes, which could have generated bias. As a result of this biased reporting, network meta-analyses could only be conducted for a restricted range of outcomes.

The study should have disclosed the findings despite the intention to do subgroup analyses or meta-regression analyses with preset covariates. The findings of each study were given as an online supplement, namely in the format of a data extraction table. The results were presented with no elucidation or juxtaposition with the comprehensive findings. More reporting is needed on how important patient characteristics affect treatment results [21]. No systematic search of grey literature was conducted; only manual searching was undertaken. The strategies for addressing concerns encountered throughout the study selection and data extraction process are not specified. The list of studies not included in the analysis has yet been provided—the analysis and results of

the study needed to consider the scientific rigor of the included studies adequately. Furthermore, there needed to be more assessment of publishing bias.

The evidence is transferable as it is relevant and applicable to the research topic “use of midodrine in hepatorenal syndrome .”Most of the articles provided information from the actual observation of evidence. Hence, the proper insight of evidence will benefit the study's different areas.

CONCLUSION

This study is beneficial for providing detailed insight into assessing the use of midodrine in hepatorenal syndrome. The study found that Midodrine has been observed to reduce the activity of nitrite and nitrate in individuals with ascites, regardless of whether they have hepatorenal syndrome (HRS). These patients also have lower plasma renin activity and reduced levels of antidiuretic hormone. This could serve as a method to reduce portal pressure and mitigate the accumulation of ascitic fluid. Thus, a new aspect has been proposed through this study.

This study did not reveal any information about the way midodrine can be improved to treat HRS patients. Moreover, numerous studies focus on the effectiveness of midodrine in curing hepatorenal syndrome. However, the efficacy and safety of the drug have been done in a limited population. More significant, well-designed clinical trials are highly required to address this issue. Most studies need to be more explicit about Optimal Dosage and Duration. Thus, studies are required to analyze any adverse effects of the drug.

This meta-analysis offers tremendous scope for future research on using midodrine in hepatorenal syndrome. There can be research on combination therapy, as midodrine can be taken in combination with other vasoconstrictor agents, such as octreotide or albumin. Moreover, the cost-effectiveness of the medication can be explored based on the outcome of this study. More research can be done on intravenous infusion of midodrine.

Word Count – Words: 5,491

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Legend: Figure 1

The PRISMA flowchart show an illustrative depiction of the examination process. After the first count of articles found, the system guarantees openness in the selection process by generating reports on the decisions made at various stages of the systematic review. Articles are recorded in detail at every stage.