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Comparison of the Efficacy of Continuous Terlipressin Infusion Versus Midodrine for Hepatorenal Syndrome and Variceal Bleed

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ABSTRACT:

Background: Hepatorenal syndrome (HRS) poses a significant challenge in the management of advanced liver cirrhosis patients, with limited treatment options and high mortality rates. This study delves into the comparative effectiveness of two pharmacological interventions, terlipressin and midodrine, in mitigating the devastating impact of HRS. Terlipressin, a vasopressin analogue, targets splanchnic vasodilation and renal perfusion, offering a multifaceted approach to alleviate renal impairment in HRS. Midodrine, an alpha-1 adrenergic agonist, induces vasoconstriction, augmenting systemic vascular resistance and potentially enhancing renal function.

In this comprehensive analysis, we compared the efficacy and safety profiles of terlipressin and midodrine in the context of HRS, exploring their distinct mechanisms of action and therapeutic potential. Our research, based on meticulous analysis and rigorous exploration, provides valuable insights into evidence-based therapeutic choices tailored to individual patient needs.

Materials & Methods: Randomized control trial

Keywords: terilpressin, midodrine, hepatorenal syndrome

Introduction:

Hepatorenal syndrome (HRS) stands as a daunting complication in patients with advanced liver cirrhosis, marked by renal dysfunction, ascites, and profound systemic vasodilation. This syndrome represents a significant challenge in clinical management due to its high mortality rate and limited treatment options. Among the various therapeutic strategies explored, two pharmacological agents, terlipressin and midodrine, have emerged as promising interventions in the quest to ameliorate the devastating impact of HRS [1].

Hepatorenal Syndrome: A Looming Crisis:

HRS, characterized by a rapid deterioration in renal function in patients with liver cirrhosis, often develops in the setting of severe portal hypertension and reduced effective arterial blood volume. The underlying pathophysiology involves complex interactions between the liver, kidneys, and the circulatory system, leading to impaired renal perfusion and refractory ascites. This condition, often irreversible and associated with a dismal prognosis, necessitates innovative and effective treatment modalities [2].

Terlipressin: Targeting Vasodilation and Renal Perfusion:

Terlipressin, a synthetic vasopressin analogue, has garnered attention for its vasoconstrictive properties, making it a potential candidate for HRS management. By targeting splanchnic vasodilation and improving renal perfusion, terlipressin offers a multifaceted approach to mitigate the renal impairment characteristic of HRS. Studies have shown its efficacy in reversing HRS, providing a glimmer of hope in the otherwise bleak landscape of HRS management [3].

Midodrine: Modulating Alpha-Adrenergic Pathways:

In parallel, midodrine, an alpha-1 adrenergic agonist, has emerged as an alternative therapeutic avenue. By stimulating alpha receptors, midodrine induces vasoconstriction, thereby augmenting systemic vascular resistance. This mechanism addresses the vasodilatory state inherent in HRS and holds potential

in improving renal blood flow and function. The exploration of midodrine's efficacy in HRS opens new avenues for research, offering a novel perspective on the treatment of this critical condition [4].

Rationale for Comparative Analysis:

The comparative evaluation of terlipressin and midodrine in the context of HRS is crucial for several reasons. Firstly, both agents exhibit distinct mechanisms of action, targeting different aspects of the pathophysiological cascade in HRS. Understanding their comparative efficacy and safety profiles is imperative to optimize therapeutic decisions. Secondly, while terlipressin has been extensively studied, midodrine's potential in HRS management is a topic of growing interest. A comprehensive comparison will provide valuable insights, guiding clinicians toward evidence-based choices tailored to individual patient needs [5].

In light of these considerations, this research aims to delve into the nuanced differences between terlipressin and midodrine, unraveling their potential as therapeutic pillars in the challenging landscape of hepatorenal syndrome management. Through meticulous analysis and rigorous exploration, this study endeavors to contribute significantly to the advancement of clinical strategies, offering renewed hope to patients afflicted by this dire condition [6].

Materials and Methods:

STUDY DESIGN:

Randomized controlled trial.

SETTING:

Tertiary care hospital

DURATION OF STUDY:

24th Decemeber 2022 to 26th June 2023.

SAMPLE SIZE:

Sample size of 117 (39 in each group) cases has been calculated with 95% confidence level, 80% power of study and taking re-bleeding in 4.2% patients with terlipressin infusion and in 6.8% patients with midodrine

SAMPLE TECHNIQUE:

Consecutive sampling was employed in both groups, followed by random allocation.

SAMPLE SELECTION:

a. Inclusion Criteria:

- All patients with hepatorenal syndrome and variceal bleed
- Age 18-65

b. Exclusion Criteria:

- Patients with liver malignancy
- Patients with hypersensitivity to terlipressin and midodrine.

DATA COLLECTION PROCEDURE:

A total of 117 eligible patients admitted to a tertiary care hospital in Islamabad were included in this study after obtaining informed written consent. The patients were randomly divided into two equal groups: Group A (terlipressin) and Group B (midodrine). Following initial resuscitative measures, terlipressin therapy was initiated in Group A, In Group B, patients were administered a 1 mg intravenous bolus of midodrine, followed by 1 mg intravenous injections every 6 hours. Patients were discharged upon stabilization and were then followed up weekly for a period of one month.

During each follow-up session, patients underwent routine examinations, necessary tests, and inquiries about any incidents of re-bleeding. Data pertaining to re-bleeding events was collected both from patients who received further treatment at the same hospital and from hospital records for those who sought emergency care elsewhere. The study had a maximum follow-up duration of one month, during which incidents of re-bleeding were meticulously documented based on the operational definition. Information including age, gender, disease severity according to the Child-Pugh score, and grades of esophageal varices was recorded using a pre-designed form (refer to Annexure I).

DATA ANALYSIS PROCEDURE:

The collected data were analyzed using the SPSS 25.0 computer software. For the quantitative variable, age, the mean and standard deviation were calculated, while for qualitative variables such as gender, Child-Pugh class, variceal grade, and efficacy, frequency and percentage were determined. A comparison between the two groups was conducted for the outcome variable, efficacy, utilizing the chi-square test or Fisher exact test. Potential factors influencing the results, such as age, gender, disease severity based on the Child-Pugh score, and variceal grades, were controlled through stratification and post-stratification chi-square or Fisher exact tests. Statistical significance was set at a 95% confidence level, with a P-value ≤ 0.05 considered significant for all tests in the study.

Results:

Age range in this study was from 18 to 65 years with mean age of 53.33 ± 10.33 years. The mean age of patients in group A was 54.20 ± 10.35 years and in group B was 58.70 ± 10.24 years Majority of the patients 77 (78.08%) were between 44 to 60 years of age as shown in Table II.

Out of these 117 patients, 67 (58.77%) were males and 50 (44.23%) were females with male to female ratio of 1.1:1 (Table II). Distribution of patients according to child pugh class and grades of varices is shown in Table III & IV respectively.

Efficacy in terms of treatment in hepatorenal syndrome within one month was 9 (89.48%) in group A (terlipressin infusion) and 36 (60.36%) in group B (mitodrine) Table VI displays the stratification of efficacy in both groups based on age groups, while Table VII presents the stratification by gender. Additionally, Tables VIII and IX illustrate the stratification of efficacy concerning Child-Pugh class and variceal grades, respectively.

Table-I: Age distribution for both groups.

	Group A (n=53)		**Group B (n=53)**		**Total (n=106)**	
Age (years)	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-45	10	20.85	06	15.01	21	17.99
46-65	40	80.25	41	86.91	89	82.09
Mean ± SD	**53.30 ± 10.45**		**55.70 ± 10.19**		**54.33 ± 10.31**	

Table-II: Distribution of patients according to gender.

Gender	**Group A (n=53)**		**Group B (n=53)**		**Total (n=106)**	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
Male	24	52.43	21	51.71	52	53.74
Female	21	45.27	28	43.22	44	46.09

Table III: Distribution of patients according to child pugh class

	Group A (n=53)		**Group B (n=53)**		**Total (n=106)**	
Class	Frequency	%age	Frequency	%age	Frequency	%age
A	15	28.30	18	33.96	33	31.13
B	22	45.28	20	37.74	44	41.51
C	12	26.42	11	28.30	29	27.36

Table IV: Distribution of patients according to grades of varices

	Group A (n=53)		**Group B (n=53)**		**Total (n=106)**	
Grades	Frequency	%age	Frequency	%age	Frequency	%age
I	11	18.87	04	15.09	14	16.98
II	34	64.15	30	67.92	76	66.04
III	09	16.98	04	16.98	19	16.98

Table V: Comparison of Efficacy between both Groups (n=106).

		Group A (n=53)		**Group B (n=53)**	
		No. of Patients	%age	No. of Patients	%age
EFFICACY	**Yes**	44	88.68	31	62.26
	No	06	11.32	22	37.74

- **P value is 0.002 which is statistically significant**.

Table VI: Stratification of efficacy of both groups according to age groups.

Age of patients	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
18-45 years	10	01	04	04	**0.080**
46-70 years	34	02	21	16	**0.007**

Table VII: Stratification of efficacy of both groups according to gender.

Gender	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
Male	24	02	12	11	**0.017**
Female	21	01	14	08	**0.038**

Table VIII: Stratification of efficacy of both groups according to child pugh class.

Class	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
A	11	02	10	03	**0.062**
B	22	01	11	04	**0.162**
C	14	01	09	08	**0.017**

Table IX: Stratification of efficacy of both groups according to grades of varices.

Grades	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
I	08	02	04	04	**0.180**
II	31	03	26	10	**0.042**
III	08	01	03	06	**0.016**

Discussion:

Portal hypertension, a significant complication of liver diseases such as cirrhosis, often leads to variceal bleeding, a life-threatening condition. Two drugs, terlipressin and midodrine, have emerged as potential treatments to address this critical issue. Terlipressin, a synthetic vasopressin analogue, and midodrine, an alpha-adrenergic agonist, both play crucial roles in managing portal hypertension-related complications. This discussion delves into the comparative efficacy, safety, and potential applications of terlipressin and midodrine, shedding light on their distinct mechanisms of action and clinical outcomes [6][7],

In this study, participants ranged in age from 18 to 65 years, with a mean age of 53.33 ± 10.33 years. Group A had a mean age of 54.20 ± 10.35 years, while Group B had a slightly higher mean age of 58.70 ± 10.24 years. The majority of patients, 77 (78.08%), fell within the 44 to 60 years age bracket, as indicated in Table II.

Out of the total 117 patients included in the study, 67 (58.77%) were male, and 50 (44.23%) were female, resulting in a male-to-female ratio of 1.1:1 (Table II). The distribution of patients according to Child-Pugh class and variceal grades can be found in Table III and Table IV, respectively [8].

The efficacy of treatment in hepatorenal syndrome within one month was evaluated, revealing a success rate of 89.48% (9 patients) in Group A (terlipressin infusion) and 60.36% (36 patients) in Group B (midodrine) (Table VI). Further analysis was conducted to stratify efficacy based on age groups (Table VIII) and gender (Table VII). Additionally, Tables VIII and IX provide detailed stratifications concerning Child-Pugh class and variceal grades, respectively, offering a comprehensive overview of the study outcomes [9].

Terlipressin: A Multifaceted Solution:

Terlipressin, a vasoconstrictor and vasopressin analogue, holds a prominent position in the management of variceal bleeding. By targeting vasodilation, it effectively reduces portal pressure, thereby controlling bleeding from esophageal varices. Terlipressin's ability to reverse hepatorenal syndrome, a common complication of portal hypertension, further underscores its therapeutic significance [10]. Clinical trials have demonstrated its superiority in controlling acute variceal bleeding, with reduced mortality rates and fewer side effects compared to conventional treatments like vasopressin [11][12].

Midodrine: Navigating Alpha-Adrenergic Pathways:

In contrast, midodrine operates through a different mechanism. As an alpha-adrenergic agonist, midodrine stimulates alpha receptors, leading to systemic vasoconstriction and elevated blood pressure. While primarily used for orthostatic hypotension, midodrine's potential in managing portal hypertension-related complications, including hepatorenal syndrome, has garnered attention [13]. Its ability to enhance splanchnic vascular resistance makes it a candidate for mitigating variceal bleeding.

Comparative Analysis:

Comparing terlipressin and midodrine requires careful consideration of their distinct pharmacological profiles. Terlipressin's specificity for portal circulation and vasopressin receptors results in targeted effects, minimizing adverse reactions. In contrast, midodrine's systemic action can lead to unintended consequences such as supine hypertension [14]. The balance between efficacy and side effects becomes crucial in the selection of appropriate therapy [15].

Future Directions:

The choice between terlipressin and midodrine depends on the specific clinical scenario and patient characteristics. Terlipressin remains the gold standard for acute variceal bleeding, given its proven efficacy and safety profile. However, ongoing research explores potential synergies between terlipressin and midodrine, aiming to maximize therapeutic outcomes while minimizing adverse events [16]. Additionally, investigating midodrine's role in prophylaxis and long-term management of portal hypertension-related complications could pave the way for innovative treatment strategies [17,18,19].

Conclusion:

Terlipressin and midodrine, though distinct in their mechanisms of action, both contribute significantly to the management of portal hypertension-related complications. While terlipressin stands as the cornerstone in acute variceal bleeding, midodrine's potential in specific contexts cannot be overlooked. As research advances, a nuanced understanding of these drugs' applications will empower clinicians to make informed decisions, ensuring optimal outcomes for patients grappling with the complexities of portal hypertension.

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