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Oral Midodrine Use in Weaning of Intravenous Vasopressor Infusions in Septic Shock Patients

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Abstract

Background: Sepsis is characterized as an infection that causes potentially fatal organ malfunction as a result of a dysregulated patient response to the infection (SSC), with septic shock being a subgroup of sepsis linked with greater fatality rates due to significant underlying metabolic, cellular, and circulatory abnormalities. This study aimed to evaluate the effects of midodrine on the weaning process off IV vasopressors as well as the drug's economic value. **Methods:** This prospective controlled trial was executed on One hundred patients with septic shock. Patients were split into two equal groups: the norepinephrine group (IV norepinephrine only): patients were given intravenous vasopressor infusion and Midodrine group: given oral midodrine 10 mg three times day, Furthermore an intravenous vasopressor (IV norepinephrine). **Results:** The midodrine group had a higher APACHE II score compared to the control group (P=0.009). Midodrine significantly reduced the requirement for HD or MV, which in turn reduced the length of time patients spent in the intensive care unit (ICU) and the associated costs. Midodrine has a beneficial effect on ICU costs. The period of intravenous injection of nor-epinephrine is favourably affected by midodrine. **Conclusions:** The study's authors state that midodrine has the potential to aid resuscitated patients with septic shock in weaning off intravenous vasopressors, which would have many economic benefits, such as reduced total expenditures and shorter stays in the critical care unit. Midodrine may be helpful in treating patients with septic shock.

Keywords: Oral Midodrine, Weaning, Intravenous Vasopressor Infusions, Septic Shock.

1.Introduction

Sepsis is described as infection with life-threatening organ dysfunction produced by the dysregulated patient response to infection (SSC), with septic shock being a subgroup of sepsis linked with greater fatality rates due to significant underlying metabolic, cellular, and circulatory abnormalities [1, 2].

Clinical manifestations of septic shock include serum lactate levels more than 2 mmol/l and persistent fluid-unresponsive hypotension that requires vasopressor support to maintain a mean arterial blood pressure (MAP) larger than 65 mm Hg, even after adequate volume resuscitation [1].

Fast initiation of fluid resuscitation, empiric antibiotic treatment, and the utilization of vasopressors in patients who remain hypotensive following the first round of fluid resuscitation within the first hour after sepsis diagnosis were all components of the one-hour bundle that the SSC delivered [3].

Weaning off intravenous (IV) vasopressors may be a challenge for some severely sick patients, even when they recover from their illness. Thus, patients who have fulfilled the criteria for ICU release are unable to be discharged due to the ongoing use of low-dose intravenous vasopressors and persistently low blood pressure [4].

Tachyphylaxis, peripheral limb ischemia, and visceral ischemia are among the consequences that might arise from not being able to completely wean patients off the IV vasopressors [5], rise in the healthcare cost, prolongation of ICU stay, delirium and ICU-acquired resistant infections and mortality [6].

Midodrine is an oral medicine that the FDA has authorised for the treatment of symptomatic hypotension [6]. The alpha-1 adrenergic agonist desglymidodrine is an active metabolite that it produces. Desglymidodrine raises vascular tone by stimulating arterial and venous alpha-adrenergic receptors; it has no direct effects on the central nervous system or the heart. Piloerection, pruritus, parathesia, and urine retention are among the most frequently reported side effects. Supine hypertension, described as a systolic blood pressure (SBP) more than 200 mm Hg, was the most severe side effect associated with midodrine. Another possible side effect of midodrine is a compensating reflex reduction in heart rate.[7].

Midodrine (10 mg, three times day) significantly raised SBP by 21.8 mm Hg in 171 patients with neurogenic orthostatic hypotension in contrast to placebo, and this effect persisted throughout the course of the trial's three weeks [8].
Midodrine is used off-label to help patients with orthostatic hypotension wean off IV vasopressor infusions by providing hemodynamic support, thanks to its predictable pharmacological response and beneficial sympathomimetic effects.[9].
This study aimed to evaluate the effects of midodrine on the weaning process off IV vasopressors as well as the drug's economic value.

2.Patients and methods

This research was a prospective controlled trial. One hundred patients with septic shock who were

resuscitated and admitted to the critical care medicine department at Benha University hospitals and who had shown clinical stability on intravenous vasopressors at low doses for at least twenty-four hours were included in the research.

Official approval was sought from the Benha University Hospitals administration and the Dean of the Benha Faculty of Medicine. All subjects provided written informed permission that included the following topics: research purpose, methodology, location, time, subjects, and measurements; confidentiality. The Benha Faculty of Medicine's Research Ethics Committee gave its permission.

Inclusion criteria were patients ranging in age from 18 to 80 years old were admitted to ICU with sepsis and septic shock, hypotensive (SB <90 mmHg and MAP<65 mmHg), and needing an intravenous vasopressor infusion for more than 24 hours to keep their target arterial blood pressure goals.

Exclusion criteria were individuals experiencing cardiogenic, obstructive, or hypovolemic shock, has a severe case of organic heart disease, an ejection fraction below 30%, and a heart rate of < 50 beats per minute, with AIDS, hereditary immunodeficiency diseases, organ transplant recipients, and those undergoing cytotoxic drug or radiation treatment all have impaired immune systems, have chronic renal disease with a blood creatinine level of 2 mg/dL or higher at baseline, individuals using medications that include ergot derivatives, such as monoamine oxidase inhibitors, alpha blockers, tricyclic antidepressants, or any other similar medication, managing bacterial endocarditis that need ongoing medication, had an adverse reaction to midodrine, prior episodes of orthostatic hypotension, administered before to admission for various purposes, midodrine, and under palliative care.

Methods:

With the help of G power sample size calculator version 3.1.9.4, the sample size was determined. One hundred patients made up the final sample size. Two groups, each including fifty patients, were randomly allocated to participate, as per the guidelines set forth by the Surviving Sepsis Campaign. Having a diagnosis of sepsis or septic shock at arrival or while hospitalised in the critical care unit was a requirement for inclusion.

Fifty patients were given intravenous vasopressor infusion as part of the first group, which was called **the norepinephrine group** (IV norepinephrine only). Fifty patients were assigned to the **Midodrine group**, which was given oral midodrine 10 mg three times day, furthermore an intravenous vasopressor (IV norepinephrine). Midodrine is a viable therapy option for individuals who have achieved clinical stabilization on low dose IV vasopressors for a minimum of 24 hours.

There will be no more norepinephrine when the systolic and mean arterial blood pressures reach 90- and 70-mm Hg, respectively. If a negative pharmaceutical response occurred or intravenous norepinephrine was discontinued, the use of midodrine was halted one to two days later. Midodrine 2.5 mg pills were administered either orally (by crushing and swallowing) or intravenously (via the Ryle tube).

Data collection

Before and after patients discontinued intravenous vasopressor use, researchers looked at their medical records for demographic and clinical information. Careful documentation of all patients' clinical data was done, including their main admission diagnosis, infection source, underlying diseases, duration of mechanical ventilation, and steroid use. We calculated APACHE and SOFA scores for both groups at baseline. All of the patient's vital signs were meticulously documented, including their arterial blood gases, lactate, coagulation profile, electrolytes, central venous pressure, electrolytes, and tests for liver and kidney function. Details such as vital signs, duration of ICU stay, and kind of intravenous vasopressors given were also documented.

The exact amounts of intravenous epinephrine to provide at the start of weaning, as well as the lowest, average, and maximum doses, and other relevant details. Furthermore, data was recorded regarding the following: the length of time from the beginning of the weaning period until the IV nor epinephrine was stopped or the patient died; the length of time the nor epinephrine was used; the average of two MAP readings taken at the beginning and end of the nor epinephrine infusion; the number of patients who required reinfusion after the discontinuation of the infusion; the length of time the use was resumed; and the number of patients readmitted to the intensive care unit following discharge.

Direct medical charges were determined from the patient's perspective using hospital computerized sheets for micro-costing. In the intervention group, the price of midodrine was part of the total daily expenditure. The economic evaluation was determined by variables such as alterations in survival, total time spent on these measures, and the time it took to wean off IV vasopressors until discharge or death.

Outcomes:

The main results were the total microgram dosage of nor epinephrine, the amount of time the patient was on intravenous nor epinephrine, and the time it took to wean off the drug. Included as secondary outcomes were the number of deaths, the average duration of stay in the ICU, and the monetary effect

of midodrine treatment throughout the recovery phase of patients with septic shock. Time to ICU release or patient death after midodrine beginning, adverse events linked to midodrine administration, and MAP at the time of commencing norepinephrine were other variables.

Statistical analysis

Using SPSS, we examined and presented the data that we gathered statistically (SPSS). Numbers and percentages were employed to display categorical data. . To depict the continuous data, the mean and standard deviation were employed. Appropriate statistical tests were employed, and a significance level of 0.05 was deemed appropriate for this study. It was deemed significant when the two-tailed P value was < 0.05.

3.Results

In terms of demographic information, no statistically significant difference was existed between the categories. Age, sex, morbidities, and infection source were all similar across the two groups. With a p-value of just 0.526, the midodrine group had an average hemoglobin level of 9.9±1.3 g/dl, whereas the control group had 10.06±1.1 g/dl. In terms of laboratory markers such as hemoglobin, total bilirubin, C-reactive protein, albumin in serum, aspartate aminotransferase, alkaline phosphatase, creatinine in serum, and urea in serum, the two groups were equally good. **Table (1)**

Table (1) Patient demographic data and lab parameters between control and midodrine groups.

		Midodrine group (N=50)	Control group (N= 50)	P-value
Age in years		60.2±9.4	59.9±10.8	0.769
Sex, Males %		21 (42%)	25 (50%)	0.547
Hypertension		26 (52%)	24 (48%)	0.842
Diabetes M		27 (54%)	27 (54%)	----
Source of infection	**Bed sores**	10 (20%)	11 (22%)	0.993
	Peritonitis	12 (24%)	1 (22%)	
	Pneumonia	11 (22%)	11 (22%)	
	UTI	17 (34%)	17 (34%)	
		Lab parameters		
Hb (g/dl)		9.9±1.3	10.06±1.1	0.526
TLC x10^3		13.1±4.9	12.9±5.4	0.336
CRP (mg/dL)		19.7±20.06	21.94±24.6	0.882
Serum Albumin (g/dl)		3.1±0.34	3.5±0.4	0.495
AST		51.3±12.8	46.32±14.9	0.832
ALT		54.3±13.8	46.16±14.6	0.393
Serum Creatinine (mg/dL)		1.1±0.2	1.004±0.2	0.124
Serum Urea (mg/dL)		24.7±4.7	24.6±4.3	0.922

Data is expressed as the mean ±SD

The midodrine group had a higher APACHE II score in contrast to the control group (P=0.009). Contrarily, the midodrine group had shorter intensive care unit stays, shorter IV nor epinephrine durations in hours, and reduced ICU costs (p=0.002, 0.001, and 0.001, respectively). Patients hospitalized to the intensive care unit who took Midodrine had a lower need for HD and Vatable Table (2).

Table (2) Comparison between both groups regarding ICU parameters, needs for HD and MV.

	Midodrine group (N=50)	Control group (N= 50)	P-value
APACHE II	18.70±5.7	18.70±5.7	0.009*
SOFA score	10.18±2.1	9.02±2.4	0.875
ICU Duration (d)	14.88±2.5	18.02±3.5	0.002*
Duration of Midodrine in days	4.88±2.5	----	-----
Duration of IV nor epinephrine in hours	7.88±2.5	13.02±3.5	0.001*
Total cost in Egyptian pounds	39400±12682.9	65100±17770.9	0.001*
Need for Hemodynamics	23 (46%)	35 (70%)	0.025*
Need for Mechanical Ventilation	19 (38%)	32 (64%)	0.016*

Data is expressed as the mean ± SD, *: significant P value.

Midodrine significantly reduced the requirement for HD or MV, which in turn reduced the length of time patients spent in ICU and the associated costs, but it had no effect on survival rates. **Table (3)**

Table (3) Means and Medians for Survival Time.

	Meana				Median			
Classification	**Estimate**	**Std. Error**	**95% Confidence Interval**		**Estimate**	**Std. Error**	**95% Confidence Interval**	
			Lower Bound	**Upper Bound**			**Lower Bound**	**Upper Bound**
Control	21.262	0.474	20.334	22.190	21.000	0.630	19.765	22.235
Midodrine	21.220	0.432	20.373	22.066	21.000	0.662	19.703	22.297
Overall	21.323	0.335	20.667	21.980	21.000	0.412	20.192	21.808

a. Estimation is limited to the largest survival time if it is censored.

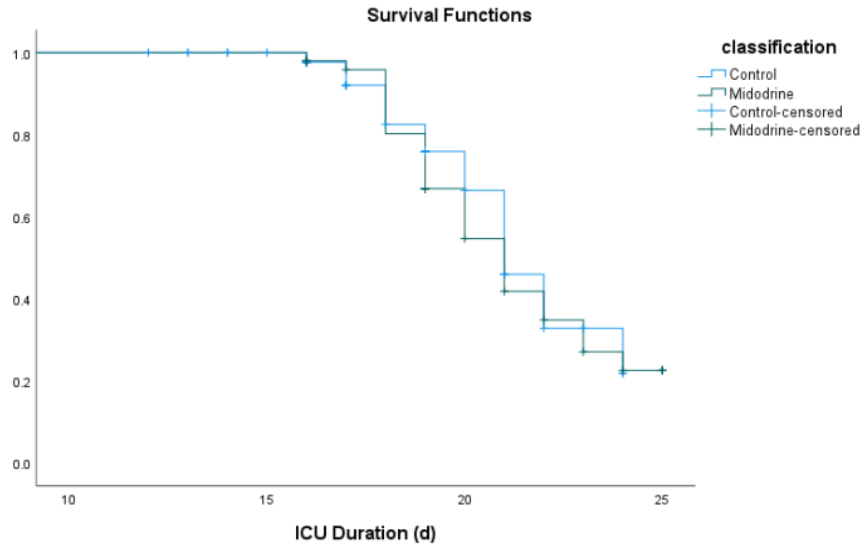

Fig () Demonstrated that neither group had a significantly different survival rate.

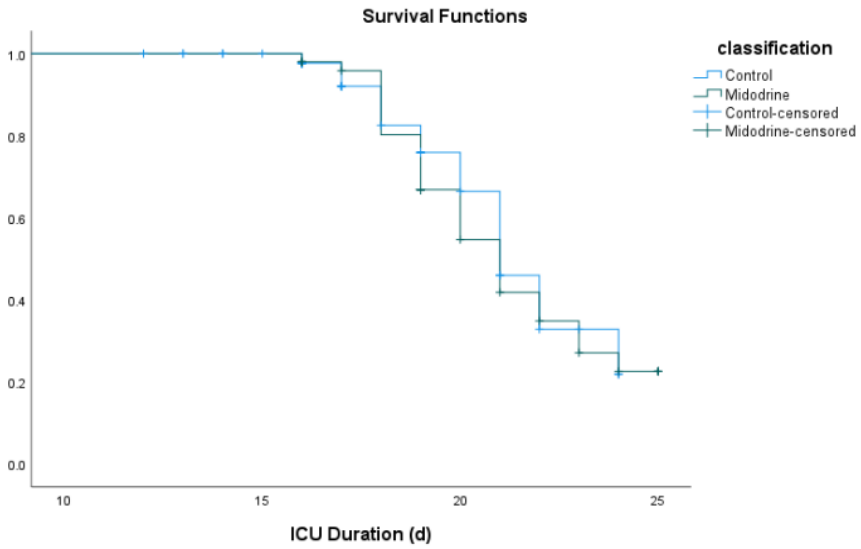

Fig (2) Kaplan Meier curve of the survival between both groups.

Using the Mann-Whitney U Test, midodrine has a beneficial effect on intensive care unit costs. **Table (4)**

Table (4) Independent-Samples Mann-Whitney U Test Summary

Total N	100
Mann-Whitney	295.500
Wilcoxon W	1570.500
Test Statistic	295.500
Standard Error	144.502
Standardized Test Statistic	-6.605
Asymptotic Sig.(2-sided test)	.000

Researching how Midodrine affects the length of time that intensive care unit (ICU) patients need IV nor-epinephrine. The duration of intravenous injection of nor-epinephrine is favourably affected by midodrine. **Table (5)**

Table (5) Independent-Samples Mann-Whitney U Test Summary

Total N	100
Mann-Whitney	295.500
Wilcoxon W	1570.500
Test Statistic	295.500
Standard Error	144.502
Standardized Test Statistic	-6.605
Asymptotic Sig.(2-sided test)	.000

4.Discussion

The majority of patients need a stay in ICU for the purpose of providing continuous monitoring and physiologic support. Intravenous vasopressors are the cornerstone of treating septic shock and other types of shock where hemodynamic support is necessary. concerning the Surviving Sepsis Campaign, norepinephrine is now the go-to medicine for treating septic shock [10].

When looking at age, sex, morbidities, and infection source, we did not find any statistically significant differences between the groups in this research. This suggests that the two groups' patient characteristics were quite similar at baseline. Both Midodrine and control groups had similar mean haemoglobin levels (9.9±1.3 and 10.06±1.1 g/dl, respectively), with a p-value of 0.526. As far as laboratory indicators including haemoglobin, total lipid profile, C-reactive protein, albumin in serum, as well as aminotransferases and urease were concerned, both groups were similar.

Basiouny al. aimed to find out whether patients with vasopressor dependent hypotension had a shorter time to withdrawal of intravenous vasopressor if they used adjunctive oral midodrine, therefore our results are in line with their findings. The researchers concluded that there was no evidence of group-specific difference in the demographics, clinical data, or hemodynamic parameters of the patients studied [11].

The current research found that the midodrine group had substantially shorter intensive care unit stays, shorter IV norepinephrine durations in hours, and lower overall ICU costs (p=0.002, 0.001, and 0.001).

The results of more recent, smaller RCTs have been shown to be statistically equivalent. Sixty patients with septic shock who were clinically stable on low-dose intravenous vasopressors were followed for at least 24 hours by Adly et al. They discovered that the duration of intravenous vasopressor medication was significantly reduced when patients were given midodrine. Still, we can't put too much stock in this study because of the tiny sample size and the absence of blinding. The midodrine group was able to save money in comparison to the norepinephrine group. But they did see that, on average, the two groups stayed about the same amount of time [12].

Poveromo et al. and Rizvi et al. came to identical conclusions in their studies. Within half an hour to two and a half days of starting midodrine, patients were gradually weaned off intravenous vasopressors; of the 94 patients admitted to the medical and surgical ICUs, 96% remained vasopressor-free [4]. A large group of patients admitted to the surgical and medical ICUs were seen by *Rizvi et al.* to have a much lower median cumulative dose of vasopressor, with 48% of those patients being able to discontinue its use within the first day [13].

Midodrine, when administered in divided doses of 20–40 mg daily, maintains MAP constant enough to permit the weaning of intravenous vasopressors, according to Sekar et al. Oral midodrine's effects were apparent within the first 48 to 72 hours, albeit

the time it took to completely wean off intravenous treatment varied from case to case [14].

The MAVERIC study was a multicenter open-label RCT that utilized identical inclusion and exclusion criteria. In contrast to the MIDAS study, the MAVERIC trial used a lower dose of midodrine (10 mg 8-hourly) and reached the same conclusions. The midodrine group required 16.5 hours (IQR, 7.5-27.5 hours) to wean off intravenous vasopressor, but the control group required 19 hours (IQR, 12.25-38.5 hours) (P = 0.32). In terms of overall hospital stays and stays in the critical care unit, there was no variation between the groups [15].

Saving money on healthcare and improving patient access might result from reducing the period of stay in ICU and hospitals by shortening the time patients need intravenous vasopressor therapy [16].

Supplemental midodrine was not associated with any adverse effects in the MAVERIC study, albeit it was safe to provide. With 62 patients receiving low-dose intravenous vasopressor therapy, the trial served as a prototype open-label RCT [15].

The findings of Basiouny et al. contradict this, because they discovered that oral midodrine during septic shock recovery failed to impact the duration or tapering of intravenous vasopressor infusions. Baseline levels were lower in the IV vasopressor + midodrine group in contrast to the IV vasopressor alone group, but the difference was not statistically significant. The IV vasopressor was administered for 139.65 ± 46.21 hours compared to 141.30 ± 79.00 hours, and the IV vasopressor weaning took 65.37 ± 13.94 hours instead of 73.20 ± 35.78 hours. Possible reasons for the results' lack of significance include the absence of a defined protocol for weaning off vasopressors in the unit and the fact that these drugs are mandatory and can only be temporarily discontinued in cases of hemodynamic instability (MAP ≤65 mmHg or SBP < 90 mmHg, low urine output < 0.5 ml/kg/h [17].

Despite the lack of correlation between midodrine use and shorter intensive care unit or hospital stays, the biggest retrospective research of its kind included 2,070 septic shock patients (209 patients who received adjunctive midodrine and 1861 patients who received intravenous vasopressor only). The group given midodrine needed intravenous vasopressor for a longer period of time [18]. Since patients with more chronic refractory vasoplegia or those who required intravenous vasopressor for greater than 7 days were included in the study, midodrine was likely given to them later in their intensive care unit stay. The overall findings of these meta-analyses raise questions about the efficacy of midodrine as a weaning aid [19].

Another retrospective research of 74 patients who had cardiothoracic surgery and were given midodrine to gradually reduce their intravenous vasopressor dosage existed no change in the mean duration of vasopressor use in contrast to a control group with similar propensity scores. It is worrisome that this study connected midodrine use to higher rates of death and longer stays in the ICU [20].

Our results were comparable to those of an earlier meta-analysis of observational studies in terms of length of stay (LOS), hospital length of stay (LOS), mortality, and LOS to ICU.conducted by Al-Abdouh et al., [21].

In addition, the utilization of adjuvant midodrine therapy with IV vasopressors was not associated with longer IV vasopressor use, hospital stays, or intensive care unit stays, according to Hamed et al. The ineffectiveness of midodrine non weaning patients off intravenous vasopressors might be due to a number of factors. One possible explanation for midodrine's ineffectiveness is the inappropriate sympathetic activity that occurs during the shock resolution phase and is associated with receptor desensitization. Also, to get the vasomotor effects needed to stop using intravenous vasopressors, greater and/or more frequent doses of midodrine are likely to be needed. In light of the short half-life of desglymidodrine, the active metabolite of midodrine, this is of the utmost importance [22].

The current investigation found that the APACHE II scores of the Midodrine group were significantly different from those of the Control group. The average APACHE II score is greater in the Midodrine group in contrast to the Control group, which may indicate that the patients using Midodrine are dealing with a more serious disease. Similarly, midodrine-treated patients had a significantly decreased median APACHE IV score (p=0.02), according to **Al-**Abdouh et al. [21].

After 24 hours (p=0.04), the midodrine group's HD and MV requirements rose from 84.50 mmHg at baseline to 88.03 mmHg [23].

The risk of hypotension rises when individuals requiring intervention for septic shock recovery cease vasopressin before norepinephrine [24].

There was no statistically significant difference in survival between the two groups, even though Midodrine significantly reduced the requirement for HD or MV, the length of time patients spent in ICU, and the associated costs.

This is in line with what Alsherif, found; he showed that patients who were randomly given midodrine (10 mg three times day) or no therapy at all had no change in ICU mortality rates [23].

Limitations: To start, it's important to note that this research only included one location, so our results may not apply to other situations. Second, a bigger multicenter trial would have provided stronger evidence due to the limited sample size. Another crucial aspect that might be addressed in future studies is the absence of evaluation of long-term outcomes or death rates in our study.

5.Conclusions

The study's authors state that midodrine has the potential to aid resuscitated patients with septic shock in weaning off intravenous vasopressors, which would have many economic benefits, such as reduced total expenditures and shorter stays in the critical care unit. Our findings suggest that Midodrine may be helpful in treating patients with septic shock, which is in line with previous studies. Additional research is required to validate our results and investigate the possible long-term consequences of Midodrine treatment.

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