Online Journal of
Clinical and Medical Case Reports

LAURIN PUBLISHERS

Mini-Review

MIDODRINE as Adjunct for Septic Shock Requiring Low Dose Vasopressor in ICU

Sourabh Kumar, Gyanendra Agrawal and Smita Sharma*

Senior Consultant, Jaypee Hospitals, India

Submission: February 24, 2025; Published: March 11, 2025

***Corresponding author:** Smita Sharma, Senior Consultant, Pulmo & Critical care, Jaypee Hospitals, Noida, Uttar Pradesh, Pin- 201304, India.

ABSTRACT

Background

In septic shock requiring low dose vasopressor (norepinephrine ≤ 10 mcg/min) for more than 24 hours discharge from ICU and hospital is delayed. Midodrine an oral alpha-1 adrenergic agonist is useful in such clinical scenario. The aim of this study is to evaluate midodrine as adjunct to standard therapy for refractory septic shock in ICU.

Method

The study is an Interventional, prospective, and randomised control trial conducted on eighty patients in ICU. The patients were randomized into midodrine (10 mg thrice daily) and control group by simple randomization by computer generated sequence after informed consent.

Discussion

Midodrine was approved by FDA in 1996 for orthostatic hypotension. Due to lack of randomized control trial, the use of midodrine to taper vasopressor in ICU is still an off-label use. The results showed decreased dose and duration of vasopressor, reduced ICU LOS, and hospital LOS in midodrine group. The ICU discharge status, hospital discharge status, readmission to the ICU, and 28 days' survival were similar in both groups. The success of oral vasopressor midodrine reduces cost of ICU treatment and increases ICU bed availability in limited health infrastructure like ours.

KEYWORDS

Midodrine, Septic shock, Alpha adrenergic agonist, Intensive care unit

INTRODUCTION

Septic shock is most common shock encountered in ICU. Midodrine is used in septic shock requiring low dose of norepinephrine (≤ 10 mcg/min) for more than 24 hrs in a well resuscitated patient causing delay in shifting of patients from ICU. Here comes the role of oral midodrine (10 mg TDS) which significantly reduces vasopressor duration, ICU length of stay (LOS) and hospital LOS. It also significantly reduces amount of vasopressor requirement rates with no significant adverse events except for few incidences of bradycardia.

Pharmacology

Midodrine is an oral prodrug which acts on alpha-1 adrenergic receptor agonist. It has bioavailability of 93% in tablet form and undergoes enzymatic hydrolysis to an active metabolite, desglymidodrine. It causes both arteriolar vasoconstriction and venoconstriction property. Oral doses of 2.5 mg led to peak plasma midodrine (0.01 mg/L) and desglymidodrine concentrations ((0.027 mg/L) within 30 and 60 minutes, respectively. AUC and Cmax increase proportionally over the dose range of 2.5 to 22.5 mg. Midodrine increases systolic blood pressure in dose-dependent manner one-hour post ingestion with a duration of action of approximately four hours after the 10 mg dose. Midodrine and desglymidodrine binding to plasma proteins is less than 30%. Midodrine is extensively metabolized via enzymatic cleavage in various tissues (including the liver) to the active moiety desglymidodrine. Midodrine and desglymidodrine are both excreted by kidneys with midodrine being cleared more rapidly than desglymidodrine (elimination half-life of 0.49 h vs of 2 to 3 h respectively). Both of them do not cross the blood-brain barrier. The safety profile of midodrine is well- established. The frequently observed adverse reactions are due to its an alpha-1 adrenergic agonist activity are supine and sitting hypertension, paraesthesia, pruritus (of the scalp), piloerection, chills, urinary urge, urinary retention, and urinary frequency. The most common and clinically relevant side effect is supine hypertension ((>180/110 mmHg)) in 6.4% patients. The risk is minimized if drug is administered at least 4 hours prior to bedtime or effect can be reverse with phentolamine, an alpha-1 specific antagonist. It lacks beta-1 adrenergic activity thereby does not cause tachycardia but parasympathetically mediated reflex bradycardia with reductions in heart rate observed in 12.8% patients within 24 hours of use [1-3].

METHOD

Design

We conducted an Interventional, prospective, and randomised controlled study in thirty-four bedded ICU of Department of Critical Care Medicine, Jaypee hospital, Noida on midodrine as an adjunctive therapy for septic shock requiring low dose vasopressor during January 2020 to September 2021 after clearance from ethical committee of our hospital. A total of 80 patients of age ≥18 years with septic shock requiring noradrenaline at doses ≤ 10 mcg/min for more than 24 hours were included in the study. The patients were randomized into midodrine (Group A) and control group (Group B) by simple randomization by computer generated sequence after informed consent from patient or relative.

Inclusion and Exclusion criteria

The inclusion criteria for the study were all patients age ≥18years with septic shock in recovering phase requiring noradrenaline infusion in doses ≤ 10 mcg/min for more than 24 hours. The patients with Bradycardia (heart rate <50bpm), pregnancy, pheochromocytoma, thyrotoxicosis and severe heart disease were excluded from the study.

Data collection

In both the groups baseline demographic variables collected included gender, age, body weight and height. Acute Physiology and Chronic Health Evaluation (APACHE) II score calculated within 24 hours of admission of patient was recorded. In both groups baseline vital signs (heart rate, blood pressure, SpO2, respiratory rate, temperature, urine output), arterial pH, lactate, serum creatinine, serum bilirubin at the time of enrolment were recorded. For both the groups the amount and duration of vasopressor use, the amount of intravenous fluid, requirement of sedation and ventilator support were recorded during the period of study. The secondary outcomes like ICU LOS, ICU discharge status (alive or dead), hospital LOS, and hospital discharge status (alive or dead), readmission to the ICU, and 28 days' survival were recorded for both groups. In intervention group midodrine was prescribed in doses of 10 mg thrice daily until termination of IV vasopressors or worsening hypotension demanding noradrenaline infusion >10 mcg/min or any adverse effect requiring discontinuation of drug.

Outcomes

The primary outcome was to evaluate the time taken to discontinue noradrenaline after initiation of midodrine. Secondary outcomes included a comparison between midodrine and control patients for the following: amount of vasopressor requirement, ICU LOS, ICU discharge status (alive or dead), hospital LOS, and hospital discharge status (alive or dead), readmission to the ICU, and 28 days' survival.

Statistical analysis

The Categorical variables were presented in the form of number and percentage (%). The quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The quantitative variables were analysed using independent t-test and Mann Whitney U Test (for the variables failing to follow Normal Distribution). The qualitative variables were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. The data entered in Microsoft EXCEL spreadsheet was analysed using of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0 and p value of less than 0.05 was considered statistically significant.

RESULTS

The groups had comparable gender distribution (Female- 45% vs 37.5% respectively, Male- 55% vs 62.5% respectively). The mean age (years), body weight (kg)and height (cm) in midodrine group (group A) was 61.78 ± 17.59, 67.53 ± 10.64, 164.3 ± 7.81 respectively and in control group (group B) was 59.43 ± 14.82, 69.38 ± 10.66,

165.8 ± 6.95 respectively with no statistically significant difference(p>0.05). The mean APACHE II score in group A (midodrine) was 11.53 ± 3.98 and in group B (control)was 10.43 ± 3.54 with no significant difference between them ((p value=0.196). The vitals at time of enrolment like mean heart rate (bpm), mean arterial pressure (mmHg), Spo2 (%), respiratory rate (per minute), temperature (Fahrenheit), urine output (mL/hour) in group A was 97.9 ± 10.51, 65.88 ± 4.1, 95.72 ± 3.2, 21.95 ± 4.67, 99.22 ± 1.03, 53.38 ± 8.27 respectively and in group B was 100.85 ± 9.37, 66.88 ± 4.15, 96.32 ± 2.73, 22.05 ± 4.16, 99.34 ± 1.03, 52.75 ± 7.92 respectively with no statistically significant difference (p>0.05). The mean pH, Lactate (mmol/L), Creatinine (mg/dL), Bilirubin (mg/dL) in group A was 7.37 ± 0.04, 2.47 ± 0.31, 0.89 ± 0.21, 0.74 ± 0.12 respectively and in group B was 7.38 ± 0.04, 2.4 ± 0.31, 0.87 ± 0.22, 0.75 ± 0.11 respectively with no statistically significant difference(p>0.05). Thereby both groups were comparable in terms of demographic distribution, APACHE score, vitals, organ function as difference between them is not statistically significant (p>0.05). The use of intravenous fluid (Mean ± SD in litters 8.65 ± 11.89 vs 7.1 ± 7.96, p value=0.496), sedation (30% vs 27.50% respectively, p value=0.80), and ventilator support (30% vs 27.50% respectively value=0.80) was comparable in group A and group B.

The average amount of noradrenaline used in group A and group B were 13.45 mg and16.46 mg respectively and the difference is statistically significant (Table 1). Thereby the average amount of vasopressor used in midodrine was statistically less than control group. The average time to vasopressor discontinuation was 2.17 days and3.19 days in group A than group B respectively and this is statistically significant. Hence there is early discontinuation of vasopressor in midodrine group (Table 2). The mean length of ICU stays was 5.93 days for group A and 7.5 days for group B (Table 3). The mean length hospital 11.65 days and 13.3 days for group A and group B respectively (Table 4). The difference in ICU and hospital length of stay is statistically significant thereby midodrine causes early discharge from ICU and hospital. The distribution of side effects was comparable between group A and B. (i.e., bradycardia- 5% vs 0%, p value=0.494). The readmission rates were comparable between group A and B (0% vs 5%, p value=0.494). The hospital discharge status and 28 days' survival were comparable between group A and B (Alive- 85% vs 90% respectively, Death- 15% vs 10% respectively, p value=0.737).

Amount of Vasopressor used(mg)	Group A (n=40)	Group B (n=40)	P value
Mean ± SD	13.45 ± 3.94	16.46 ± 6.43	0.013*

Table 1: Amount of Vasopressor used (mg) group A & B. (Mann Whitney U test).

Time to vasopressors discontinuation (days)	Group A (n=40)	Group B (n=40)	P value
Mean ± SD	2.17 ± 0.94	3.19 ± 1.95	0.004*

Table 2: Time to vasopressors discontinuation (days) group A & B. (Independent two-samples t-test).

Length of stay in ICU (days)	Group A (n=40)	Group B (n=40)	P value
Mean ± SD	5.93 ± 1.91	7.5 ± 2.96	0.017*

Table 3: Length of stay in ICU (days) group A& B. (Mann Whitney U test).

Length of stay in hospital (days)	Group A (n=40)	Group B (n=40)	P value
Mean ± SD	11.65 ± 2.46	13.30 ± 3.67	0.034*

Table 4: Length of stay in hospital (days) group A & B. (Mann Whitney U test).

DISCUSSION

The use of midodrine to help patients wean off or avoid IV vasopressors can address the issues of increasing cost of treatment in intensive care unit (ICU) and scarcity of bed in ICU. In midodrine group the dose and duration of vasopressor requirement was significantly less than control group. The decrease in dose and duration of inotropes also saves patients from adverse effect of vasopressors like arrhythmia, angina, acute myocardial infarction, hyperlactatemia, local tissues necrosis from extravasation. The use of oral vasopressor like midodrine also decreases need of central line insertion for vasopressor administration. Thereby decreasing complications like central line associated bloodstream infection (CLABSI), pneumothorax and hematoma during insertion. The mean length of ICU and hospital stay was significantly less in midodrine than control group. The readmission, hospital discharge status and 28 days' survival were similar in both groups. There are few limitations of our study. The highlight of this study is first randomized control trial in specific subset of ICU patients that is septic shock showing statistically significant advantage of using midodrine. The previous study showing comparable results had certain limitations. Levine et al. observed significantly rapid weaning of IV vasopressor post-midodrine administration during the first four doses of midodrine compared to pre-midodrine administration (-2.20 ± 2.45 mcg/min per hour vs. -0.62 ± 1.40 mcg/min per hour, p=0.012). It was prospective, observational study on twenty adult surgical ICU patients with absence of a control group [5]. Whitson et al. study showed decreased duration of vasopressor with midodrine (3.8 days for control group vs. 2.9 days for midodrine, p<0.001). However, it was a retrospective observational study in which administration, dosing, and tapering of midodrine was not protocol driven and the doses were gradually increased unless discontinuation of IV vasopressor [6]. Rizvi et al. showed results in favour of midodrine, but it is single-centre retrospective case series which included patients of widely ranging etiologies, lacked control group and the dose response relationship could not be inferred owing to varying dosage of midodrine [4]. Poveromo et al. showed median time to discontinue vasopressors after midodrine initiation 1.2 days, IQR 0.5–2.8. The major limitation of the study was its retrospective design, small sample size and use of midodrine in patients often requiring systemic corticosteroids and multiple IV vasopressors [3]. Peter Santer et al. MIDAS trial, multicentre randomized control trial concluded that midodrine did not decrease time to vasopressor discontinuation or length of stay in the ICU or hospital. The use of midodrine, however, resulted in more bradycardic events. However, this trial included all the hypotensive patients in ICU not specific subset of

septic patients in ICU [7]. The recent randomized control trial by Dina Hussein El Adly et al. showed decrease in vasopressor duration and mortality benefit in midodrine group in septic shock patients [8]. However, our study also has few limitations. The first limitation is small sample size and absence of blinding. The second limitation is blood pressure targets for initiation, escalation, or weaning of IV vasopressors are not standardized but depended on cardio renal status of individual patients. The third limitation is use of fixed drug dosing (10 mg thrice daily). The use of lower or higher doses of midodrine on weaning from inotropes could not be evaluated.

CONCLUSION

The use of oral midodrine as an adjunct to wean IV vasopressors in the ICU setting is an off-label use. Ours Interventional, prospective, and randomised controlled study showed results in favour of use of midodrine in septic shock patients requiring norepinephrine (≤ 10 mcg/min) with good safety profile. Midodrine by reducing the time of vasopressor weaning and reducing ICU LOS reduces cost of ICU treatment and increases ICU bed availability in limited health infrastructure like ours. We propose for a multicentre randomized control trial in India for midodrine as adjunct to vasopressor in septic patient in ICU, so that drug can be approved for use by FDA as labelled indication of use. The trial can be further extended to use of oral midodrine for sepsis patients in ward.

REFERENCES

1. McTavish D, Goa KL (1989) Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. Drugs 38(5): 757-777.
2. Zachariah PK, Bloedow DC, Moyer TP, Sheps SG, Schirger A, et al. (1986) Pharmacodynamics of midodrine, an antihypotensive agent. Clin Pharmacol Ther 39(5): 586-591.
3. Poveromo LB, Michalets EL, Sutherland SE (2016) Midodrine for the weaning of vasopressor infusions. J Clin Pharm Ther 41(3): 260-265.
4. Rizvi MS, Trivedi V, Nasim F, Lin E, Kashyap R, et al. (2018) Trends in Use of Midodrine in the ICU: A Single-Center Retrospective Case Series. Crit Care Med 46(7): e628-e633.
5. Levine AR, Meyer MJ, Bittner EA, Berg S, Kalman R, et al. (2013) Oral midodrine treatment accelerates the liberation of intensive care unit patients from intravenous vasopressor infusions. J Crit Care 28(5): 756-762.
6. Whitson MR, Mo E, Nabi T, Healy L, Koenig S, et al. (2016) Feasibility, Utility, and Safety of Midodrine During Recovery Phase from Septic Shock. Chest 149(6): 1380-1383.
7. Santer P, Anstey MH, Patrocínio MD, Wibrow B, Teja B, et al. (2020) MIDAS Study Group. Effect of midodrine versus placebo on time to vasopressor discontinuation in patients with persistent hypotension in the intensive care unit (MIDAS): an international randomised clinical trial. Intensive Care Med 46(10): 1884-1893.
8. Dina Hussein El Adly, Naglaa Samir Bazan, Radwa Maher El Borolossy, Islam Fawzy Anan, Mohamed Amin Fakher, et al. (2022) Midodrine improves clinical and economic outcomes in patients with septic shock: a randomized controlled clinical trial. Ir J Med Sci 191(6): 2785-2795.