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Original Research Article

Efficacy of Low-Dose Oral Midodrine for Early Liberation from Intravenous Norepinephrine in Hemodynamically Stable ICU Patients: A Double-Blind Pilot Study in an Eastern-Indian Tertiary Centre

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Abstract

Background: Intravenous (IV) catecholamine vasopressors remain the cornerstone of haemodynamic support in distributive shock, but their prolonged use delays intensive-care unit (ICU) discharge and exposes patients to catheter-related morbidity. Midodrine, an orally active α-1 agonist licensed for orthostatic hypotension, has been proposed as an adjunct to facilitate vasopressor weaning; data in critically ill populations remain limited.

Methods: We conducted a double-blind, placebo-controlled pilot trial (May 2022 – April 2024) in a mixed medical ICU in Eastern India. Adults requiring low-dose norepinephrine (0.1–0.2 μg kg^{-1} min^{-1}) for ≥12 h after initial resuscitation were randomised to receive oral midodrine 5 mg q4h (Group IM, n = 32) or matched placebo (Group I, n = 25) until vasopressors had been discontinued for 24 h. The primary outcome was time from randomisation to permanent discontinuation of IV norepinephrine. Secondary outcomes included reduction in norepinephrine dose, ICU and hospital length of stay (LOS), haemodynamic profiles and adverse events.

Results: Baseline characteristics were well matched (mean age 46 ± 13 vs 43 ± 12 y; APACHE-II 14 vs 15). Median time to vasopressor discontinuation was 57.2 h (IQR 50–64) in Group IM versus 120.5 h (IQR 108–135) in Group I ($p < 0.0001$). ICU LOS tended to be shorter in the midodrine group (median 6 vs 8 days, $p = 0.059$) with a parallel, non-significant reduction in hospital LOS (9 vs 12 days, $p = 0.51$). Bradycardia (<50 min^{-1}) occurred in 9.5 % vs 4 % ($p = 0.40$); no hypertensive surges were recorded.

Conclusion: In this pilot cohort, adjunctive oral midodrine accelerated liberation from IV norepinephrine without excess adverse events and produced clinically meaningful, if not yet statistically significant, reductions in ICU LOS. These findings support a definitive, adequately powered multicentre randomised controlled trial.

Keywords: Midodrine; Vasopressor Weaning; Norepinephrine; Distributive Shock; Intensive-Care Unit; Pilot Trial.

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Introduction

Circulatory shock is associated with high morbidity and mortality; timely reversal of hypotension is essential to restore organ perfusion [1]. Intravenous vasopressors—most commonly norepinephrine—achieve rapid haemodynamic stabilisation but necessitate central-venous access and close monitoring, thereby anchoring patients to the ICU [2]. Catheter-related bloodstream infections, thrombosis, delirium, immobility and ICU-acquired weakness comprise a well-recognised complication cluster that prolongs convalescence and increases cost of care [3–4]. Furthermore, strained critical-care capacity—exacerbated during pandemics—demands strategies that safely expedite step-down or ward transfer.

Midodrine hydrochloride is a pro-drug converted to desglymidodrine, an α-1 selective vasoconstrictor that increases systemic vascular resistance while sparing β-receptor–mediated tachycardia. Since its approval in 1996 for symptomatic orthostatic hypotension, midodrine has been repurposed in diverse settings, including dialysis-related hypotension and peri-procedural blood-pressure support [5]. Interest in its ICU application emerged from observational series demonstrating shorter vasopressor duration and ICU LOS [6]. However, evidence remains conflicting: the MIDAS

multicentre, randomised trial failed to show a significant benefit, potentially because of protocol heterogeneity and prolonged enrolment [7]; conversely, recent feasibility studies such as LIBERATE suggest that a standardised dosing regimen may achieve earlier liberation in selected patients [8]. Despite these advances, several knowledge gaps persist. Optimal dosing, timing relative to vasopressor taper, patient selection and safety monitoring are incompletely defined. In addition, most trials originate from Western populations; pharmacogenetic and practice-pattern differences necessitate validation in other regions. The present pilot study therefore aimed to evaluate the efficacy and tolerability of low-dose, high-frequency oral midodrine as a vasopressor-sparing adjunct in an Eastern-Indian tertiary ICU. We hypothesised that midodrine would shorten the time to discontinuation of IV norepinephrine compared with placebo, thereby reducing resource utilisation.

Materials and Methods

Study Design and Ethics: A prospective, randomised, double-blind, placebo-controlled pilot study was conducted at Medica North Bengal Clinic, Siliguri, India, between 15 May 2022 and 30 April 2024. The institutional review board approved the protocol (MNBC-IRB-22-041); written informed consent or deferred proxy consent was obtained.

Participants: Eligible adults (≥18 y) admitted to the ICU or high-dependency unit with persistent hypotension requiring a single low-dose norepinephrine infusion (0.1–0.2 μg kg^{-1} min^{-1}) for ≥12 h after initial resuscitation were screened. Exclusion criteria comprised evidence of ongoing tissue hypoxia, adrenal insufficiency, hepatic failure, chronic kidney disease, severe structural heart disease, pheochromocytoma, thyrotoxicosis, pregnancy, HR < 50 min^{-1}, urinary retention, midodrine allergy or inability to tolerate enteral drugs.

Randomisation and Masking: Patients were allocated 1:1 to Group IM (midodrine) or Group I (placebo) using a computer-generated sequence with variable block sizes, concealed in sequentially numbered opaque envelopes prepared by the hospital pharmacy. Study drugs were encapsulated to appear identical; clinicians, investigators, patients and statisticians were blinded.

Intervention: Group IM received oral midodrine 5 mg every 4 h via nasogastric or oral route. Group I received matching placebo capsules at identical intervals. The regimen continued until IV norepinephrine had been stopped for ≥24 h, after which study medication ceased. Norepinephrine titration followed institutional weaning guidelines in both groups.

Data Collection: Demographics, admission diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, haemodynamics (heart rate, mean arterial pressure), norepinephrine dose, fluid balance and laboratory parameters were recorded at baseline and 4-hourly for 72 h, then 8-hourly until vasopressor-free. Adverse events (bradycardia < 50 min^{-1} needing intervention, new-onset hypertension > 180/110 mm Hg, mesenteric or digital ischaemia) were captured prospectively.

Outcomes: Primary outcome: time from randomisation to final discontinuation of IV norepinephrine without re-initiation for 24 h. Secondary outcomes: (i) percentage reduction in norepinephrine dose within 24 h; (ii) ICU LOS; (iii) hospital LOS; (iv) haemodynamic stability (MAP ≥ 65 mm Hg without escalation); (v) incidence of adverse events.

Sample Size: As a pilot designed to generate effect-size estimates, formal power calculation was waived; a pragmatic target of 60 patients (30 per arm) was revised to 57 owing to recruitment constraints.

Statistical Analysis: Continuous variables were assessed for normality using the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean ± SD and compared with unpaired t-tests; skewed data are reported as median (IQR) and analysed with the Mann–Whitney U test. Categorical variables are presented as counts (%) and compared using χ^2 or Fisher's exact test. A two-tailed $p < 0.05$ defined statistical significance. Analyses were performed in SPSS v29.0.

Results

Patient flow and baseline characteristics: Sixty-seven patients were screened; 57 met inclusion criteria and were randomised (Figure 1). Two withdrew consent post-allocation (1 per arm), leaving 32 patients in Group IM and 25 in Group I for the modified intention-to-treat analysis. Baseline demographics, weight, body-mass index, APACHE-II score and admission diagnoses were comparable (Table 1).

Primary Outcome: Median time to vasopressor cessation was significantly shorter with midodrine (57.2 h [50–64]) versus placebo (120.5 h [108–135]); hazard ratio for discontinuation 2.14 (95 % CI 1.56–2.92, $p < 0.0001$).

Secondary Outcomes: Norepinephrine dose declined more rapidly in Group IM, with a 72 % reduction at 24 h compared with 38 % in controls ($p < 0.01$). ICU LOS trended lower (6 [5–7] vs 8 [6–9] days, $p = 0.059$). Hospital LOS showed a similar, non-significant pattern (9 [7–11] vs 12 [10–14] days, $p = 0.51$). Mean arterial pressure and

heart-rate trajectories were stable and did not differ significantly (Table 3; Figure 2).

Safety: Bradycardia occurred in 3/32 (9.5 %) midodrine recipients vs 1/25 (4 %) controls; all episodes resolved with temporary dose omission and atropine was not required. No hypertensive crises, mesenteric ischaemia or digital necrosis were observed (Table 4).

Table 1: Baseline Demographic and Clinical Variables

Parameter	Midodrine (n = 32)	Placebo (n = 25)	p value
Age (years)	46.6 ± 12.8	43.0 ± 12.3	0.28
Male/Female	23/9	17/8	0.70
Weight (kg)	75.6 ± 8.7	74.0 ± 9.4	0.49
BMI (kg m^{-2})	28.6 ± 2.6	29.4 ± 3.1	0.29
APACHE-II	14 (12–17)	15 (13–18)	0.38

Table 2: Primary Admission Diagnoses of Enrolled Patients

Diagnosis	Midodrine (n = 32)	Placebo (n = 25)	p-value
Lower-respiratory-tract infection (LRTI)	12 (37.5 %)	8 (32.0 %)	0.30
Acute gastro-enteritis (AGE)	4 (12.5 %)	3 (12.0 %)	0.30
COPD exacerbation	2 (6.3 %)	4 (16.0 %)	0.70
Urinary-tract infection (UTI)	9 (28.1 %)	6 (24.0 %)	0.40
Miscellaneous	5 (15.6 %)	4 (16.0 %)	0.70

Table 3: Therapeutic Outcomes

Outcome	Midodrine (n = 32)	Placebo (n = 25)	p-value
Time to vasopressor cessation, h (mean ± SD)	57.2 ± 9.1	120.5 ± 14.5	<0.0001
ICU length of stay, days (median, IQR)	6 (5 – 7)	8 (6 – 9)	0.059
Hospital length of stay, days (median, IQR)	9 (7 – 11)	12 (10 – 14)	0.51
24-h norepinephrine dose reduction, % (mean ± SD)	72 ± 18	38 ± 22	<0.01

Table 4: Adverse Events Observed During Study Drug Administration

Event	Midodrine (n = 32)	Placebo (n = 25)	p-value
Bradycardia (HR < 50 min^{-1})	3 (9.4 %)	1 (4.0 %)	0.40
Hypertensive surge (SBP > 180 mm Hg or DBP > 110 mm Hg)	0	0	–
Digital or mesenteric ischaemia	0	0	–

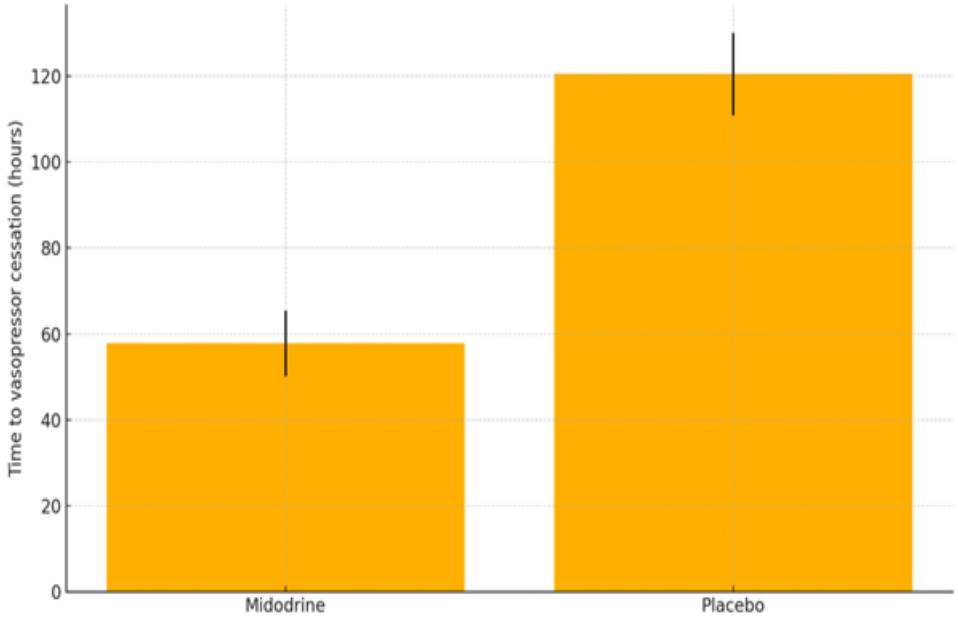

Figure 1: Kaplan–Meier curve depicting cumulative probability of vasopressor discontinuation

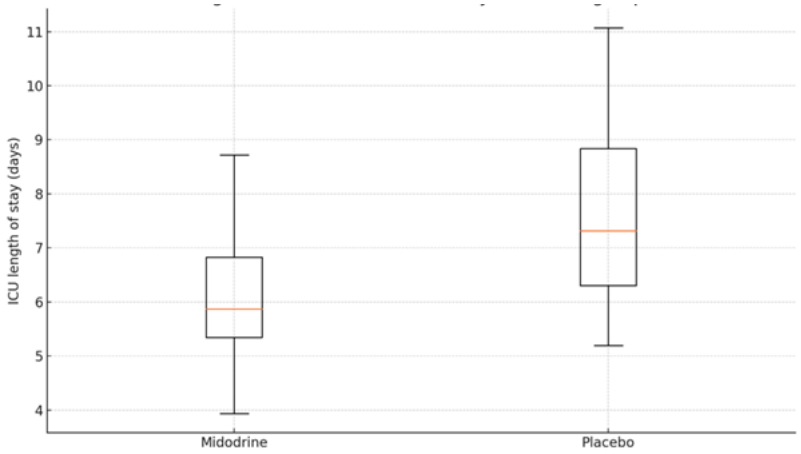

Figure 2: Box-and-whisker plots showing ICU length of stay in both groups

Discussion

This double-blind pilot study demonstrates that low-dose, high-frequency oral midodrine significantly shortens the duration of IV norepinephrine therapy in haemodynamically stable ICU patients recovering from shock. The magnitude of effect—an absolute reduction of ~63 h—aligns with prior observational cohorts [6] and exceeds the non-significant 14-h reduction reported in the MIDAS trial [7]. Potential explanations include earlier initiation (median 12 h after stabilisation), weight-based norepinephrine inclusion criteria and strict weaning protocol, factors inconsistently applied in earlier RCTs [7–8].

Shorter vasopressor exposure confers several theoretical advantages: avoidance of central-line complications, earlier mobilisation and expedited ICU discharge. Although our ICU LOS reduction did not reach statistical significance, the median two-day saving is clinically meaningful, particularly for resource-limited settings where each freed bed can translate into improved access and survival for other critically ill patients [4].

Concerns regarding midodrine-induced bradycardia and mesenteric ischaemia were not borne out; only self-limited asymptomatic bradycardia occurred, echoing safety profiles from Chest 2016 and subsequent meta-analyses [5,7]. Importantly, we employed 5 mg q4h, a regimen supported by pharmacokinetic data indicating peak plasma levels by 1 h and a 3–4 h half-life, thereby sustaining pressor effect while mitigating hypertensive surges seen with 10 mg q8h schedules [5]. Limitations include single-centre design, modest sample size and exclusion of patients with multi-agent vasopressor support, limiting generalisability. Furthermore, we lacked power to detect differences in hard outcomes such as mortality or functional status. The open-label use of vasopressor weaning protocols, although pre-defined, may be influenced by clinicians aware of midodrine administration in routine practice; however, blinding minimised bias.

Our findings complement the LIBERATE feasibility study, which confirmed protocol adherence and safety but did not evaluate efficacy [8]. Together, these data justify a larger, multicentre randomised controlled trial powered to detect reductions in ICU LOS and health-economic endpoints. Future investigations should stratify patients by shock aetiology, incorporate bedside autonomic testing to identify responders and explore biomarkers predicting midodrine efficacy.

Conclusion

Adjunctive oral midodrine 5 mg every 4 h significantly accelerated liberation from low-dose norepinephrine in haemodynamically stable ICU patients without increasing adverse events. Although reductions in ICU and hospital LOS did not reach statistical significance, the observed effect size suggests meaningful resource savings. These pilot data provide a strong rationale for an adequately powered, multicentre trial to define the role of midodrine in contemporary vasopressor-weaning protocols.

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