




Oral Midodrine as an Adjunct in Rapid Weaning of Intravenous Vasopressor Support in Spinal Cord Injury

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Abstract

Background Majority of acute cervical spinal cord injury end up requiring long-term stay in intensive care unit (ICU). During the initial few days after spinal cord injury, most patients are hemodynamically unstable requiring intravenous vasopressors. However, many studies have noted that long-term intravenous vasopressors remain the main reason for prolongation of ICU stay. In this series, we report the effect of using oral midodrine in reducing the amount and duration of intravenous vasopressors in patients with acute cervical spinal cord injury.

Materials and Methods Five adult patients with cervical spinal cord injury after initial evaluation and surgical stabilization are assessed for the need for intravenous vasopressors. If patients continue to need intravenous vasopressors for more than 24 hours, they were started on oral midodrine. Its effect on weaning of intravenous vasopressors was assessed.

Results Patients with systemic and intracranial injury were excluded from the study. Midodrine helped in weaning of intravenous vasopressors in the first 24 to 48 hours and helped in complete weaning of intravenous vasopressors. The rate of reduction was between 0.5 and 2.0 µg/min.

Conclusion Oral midodrine does have an effect in reduction of intravenous vasopressors for patients needing prolonged support after cervical spine injury. The real extent of this effect needs to be studied with collaboration of multiple centers dealing with spinal injuries. The approach seems to be a viable alternative to rapidly wean intravenous vasopressors and reduce duration of ICU stay.

Keywords

- ▶ cervical spine injury
- ▶ neurogenic shock
- ▶ neurointensive care
- ▶ refractory hypotension
- ▶ spinal cord injury

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Introduction

In a study assessing the temporal trend of vasopressor usage in critical care, it is noted that approximately 27% of patients in critical care admitted in intensive care unit (ICU) require vasopressor during their ICU stay and for most of them it remains the main barrier to decide about discharge¹. Majority of patients with cervical and upper thoracic cord injury end up having cardiovascular instability needing urgent and long-term ICU.² The most frequent and acute cardiovascular consequence is disordered blood pressure control. This has significant ramifications as cord injured people have an increased risk of developing heart disease and stroke and more importantly persistently low blood pressure will result in hypoperfusion of the injured spinal cord and exacerbate the effects of primary injury and inflammation.³ According to the available guidelines, target mean arterial pressure (MAP) of 85 mm Hg for the first 5 days is suggested to maintain cord perfusion at the injured level.⁴ A recent review by Yue et al on studies of vasopressor use in acute spinal cord injury suggested results favoring noradrenaline over dopamine or phenylephrine.⁵ Various studies have observed that prolonged and severe hypotension is possible for up to 5 weeks from the time of injury thus requiring long-term vasopressor support.²

Many patients although becoming neurologically stable will end up staying in ICU for long time for the management of hypotension alone. One possible solution to this problem is the replacement of the intravenous vasopressor with an oral agent to facilitate an earlier discharge from the ICU. Several medications have been used for this purpose (midodrine, pseudoephedrine, and droxidopa), though all are off label uses.^{6,7} Of them oral midodrine already has established usage in orthostatic hypotension and has a better evidence base with ICU studies in setting of septic shock. The current series reports the relation between oral midodrine and time to withdraw intravenous vasopressors. It explores the possibility of oral midodrine use in traumatic spinal cord injury patients to replace long-term intravenous vasopressors.

Materials and Methods

Patients who were admitted in ICU for acute cervical spinal cord injury during the period June 2020 to July 2021 were retrospectively reviewed. Standard management protocol for traumatic spinal cord injury includes routine clinical examination, imaging of spine, focused ultrasound of the abdomen, computed tomography brain, and imaging of chest, pelvis, and long bones, to rule out other systemic injuries and surgical stabilization of the spine fracture (► Fig. 1).

After surgical stabilization, clinically stable adults aged 18 years or older with intractable hypotension but 8 µg/min or less of noradrenaline infusion/equivalent vasopressor were deemed to be in intractable hypotension and started on oral midodrine for early weaning of intravenous vasopressors. The end-point of the treatment is determined as complete weaning of intravenous vasopressors. Oral midodrine was started initially at 5 mg per dose thrice a day and

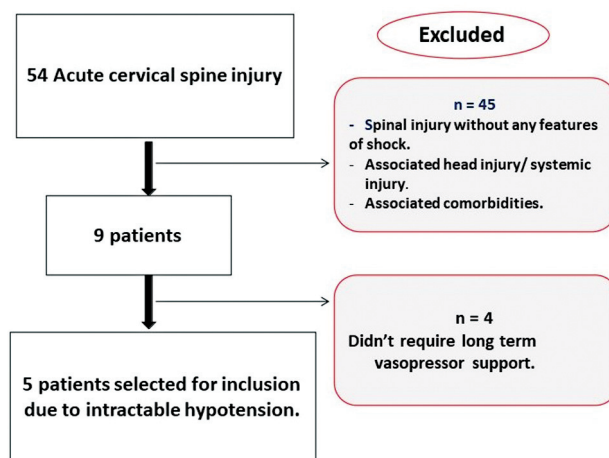


Fig. 1 Patient selection for midodrine.

depending on the response titrated according to response till intravenous vasopressors were weaned off completely.

Results

Between June 2020 and July 2021, about 54 patients with acute cervical spinal cord injury were referred to the department. Of them, 45 patients were excluded due to spinal cord injury without any features of shock, associated systemic injuries and head injury, and presence of other comorbidities. Of the remaining nine patients, four did not require long-term inotropes after surgical stabilization. The remaining five patients had intractable hypotension according to the study definition, resisting weaning from intravenous inotropes. All the five patients are male patients aged between 30 and 42 years. All of them had sustained complete spinal cord injury (ASIA), four of them in the subaxial spine and one patient with traumatic atlantoaxial subluxation. All four patients with subaxial spine injury underwent circumferential fusion of the involved level with spinal canal decompression. In case of traumatic atlantoaxial injury, he had undergone C1/C2 fixation. The patients detailed demographics and clinical details are listed in ► Table 1.

The response to midodrine as measured by the rate of reduction in intravenous vasopressors varied between

Table 1 Patient characteristics (n = 5)

| Sl. no | Age (y) | Sex | Level of injury | ASIA grade | Surgery |
|--------|---------|-----|-----------------|------------|--|
| 1 | 42 | M | C1-C2 | A | C1/2 fixation and fusion |
| 2 | 30 | M | C5-C6 | A | Circumferential decompression and fixation |
| 3 | 40 | M | C5-C6 | A | Circumferential decompression and fixation |
| 4 | 32 | M | C4-C5 | A | Circumferential decompression and fixation |
| 5 | 34 | M | C6-C7 | A | Circumferential decompression and fixation |

cases. The rate of reduction ranges widely between -0.45 and -2.0 $\mu\text{g}/\text{min}$. The rate of reduction does not depend on the amount of initial intravenous vasopressor requirement. The total duration to completely wean off intravenous vasopressor is between 1 and 14 days and does not depend on any predictive variable. One patient had asymptomatic bradycardia that was

managed by temporarily withdrawing midodrine and switching over to noradrenaline. There was no other side effects noticed. The duration of stay in ICU varied between 1 and 4 weeks due to need for mechanical ventilation. The trend of reduction in intravenous vasopressors for each patient is shown in **Fig. 2**. The results are summarized in **Table 2**.

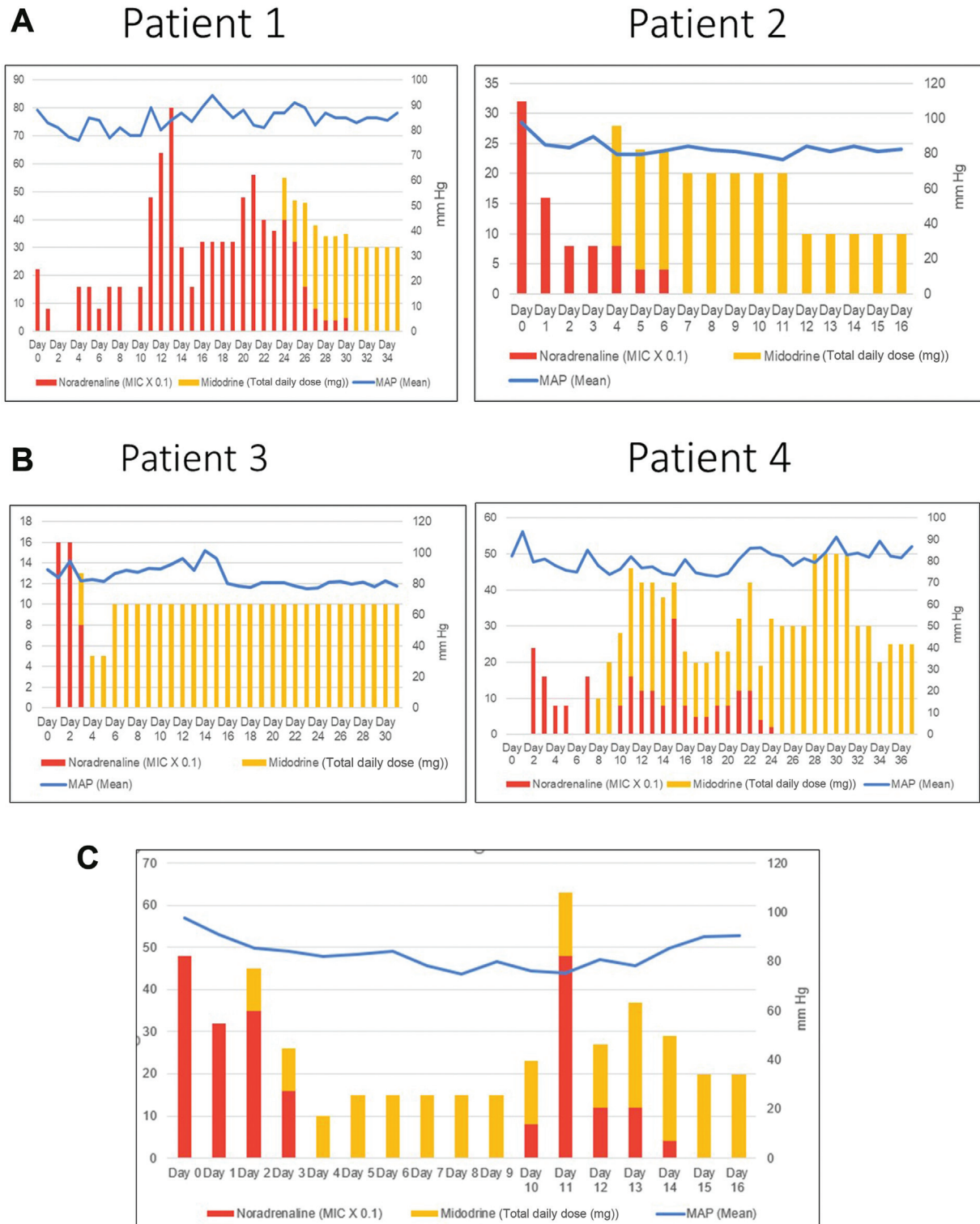


Fig. 2 (A–C) Individual patient blood pressure trend. MAP, mean arterial pressure.

Table 2 Individual response to oral midodrine

| Patient no. | Duration of ICU stay (days) | Total NE (µg) | Rate of reduction in IV NE after midodrine (µg/min) | Duration to wean off from IV NE (days) | Dose of midodrine at weaning (in mg) |
|-------------|-----------------------------|---------------|---|--|--------------------------------------|
| Patient 1 | 36 | 185,510.4 | -1.1 | 6 | 30 |
| Patient 2 | 6 | 19,200 | -0.45 | 3 | 20 |
| Patient 3 | 21 | 9,600 | -1.3 | 1 | 5 |
| Patient 4 | 16 | 53,664 | -0.59 | 14 | 30 |
| Patient 5 | 13 | 48,960 | -2.0 | 4 | 10 |

Abbreviations: ICU, intensive care unit; IV, intravenous; NE, noradrenaline.

Discussion

Acute spinal cord injury is defined as a traumatic injury of the spinal cord that results in a varying degree of paralysis to motor, sensory, and autonomic nervous.⁸ At the cellular level, there is disruption of neuronal homeostasis, apoptosis, and tissue destruction resulting in various complications of spinal cord injury. Once considered lethal with the drastic evolution of our knowledge on biomechanics of spine injury and the pathophysiology of the disease has helped in improving patient outcomes significantly.⁹ The major bulk of the available clinical literature in spinal cord injury focuses on the role of steroids, timing of surgical decompression, the optimal anti-coagulation in the post-injury phase, the role of imaging in clinical decision making and prognostication, and the type and timing of rehabilitation after acute spinal cord injury.¹⁰ All these efforts aim mainly to mitigate the actual damage to the functional neurons of spinal cord. However, there are large areas of the field that remain less understood and without any focused studies to provide good evidence.¹¹ Cardiovascular dysfunction after spinal cord injury both acute and chronic

effects are understudied. A study by Ruiz et al assessing the incidence and natural progression of neurogenic shock following traumatic spinal cord injury suggests a significant number of cases have drop in MAP after cessation of vasopressor during MAP targeted therapy after the first 5 days. These patients end up requiring prolonged vasopressor support.¹² In this study out of 54 patients, 9 patients needed intravenous vasopressors and only 5 patients (10%) required long-term vasopressors. Most of the available vasopressors in acute stage are intravenous and require intensive care support.

Midodrine is an orally available alpha-1 agonist, approved for the treatment of patients with chronic orthostatic hypotension that significantly impairs their daily activities of living. Midodrine has previously been evaluated in a variety of clinical settings, including the management of orthostatic hypotension, neurocardiogenic syncope, dialysis-induced hypotension, as a substitute for albumin in abdominal paracentesis-related hypotension and in postoperative settings for carotid artery stenting and spinal surgery.¹³⁻¹⁶ Midodrine acts in peripheral blood vessels causing vasoconstriction and consequent increase in blood pressure (► Fig. 3).

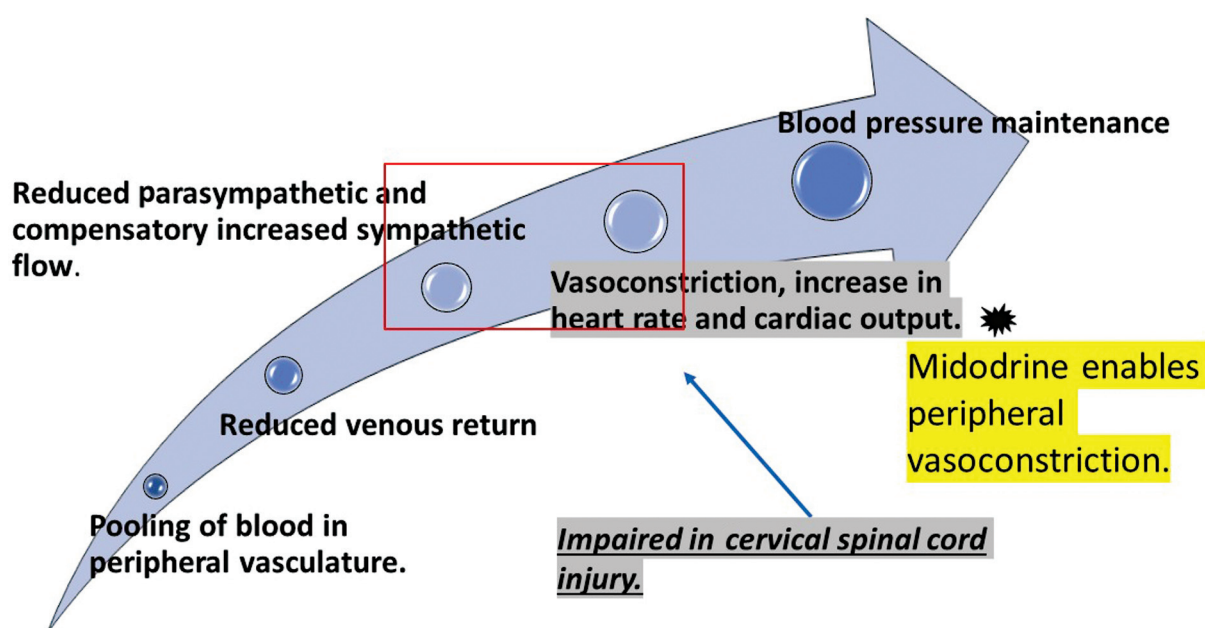


Fig. 3 Mechanism of action of midodrine.

Table 3 Summary of recent studies on oral midodrine in weaning intravenous vasopressors

| Study | n | Design | Location | Midodrine dose | Results |
|-----------------------------------|-----|-------------------------------------|------------------------|---|---|
| Levine et al 2013 ²¹ | 20 | Prospective, observational | SICU | 5–20 mg three times a day | Greater decline in vasopressor dosing |
| Whitson et al 2016 ²² | 275 | Retrospective | | 10–40 mg three times a day for 6.2 days | Shorter duration of vasopressors |
| Poveromo et al 2017 ²³ | 94 | Retrospective | CICU, SICU, NICU, MICU | 2.5–10 mg up to 6 times a day for 4.4 days | Vasopressors discontinued early |
| Rizvi et al 2018 ²⁴ | 663 | Retrospective | SICU, MICU | 5–30 mg three times a day for up to 21 days | 48% weaned off vasopressors at 24 hours |
| MIDAS trial 2020 ¹⁹ | 132 | Prospective, placebo controlled RCT | SICU, MICU | 20 mg q8h for 3 days | No difference in time to vasopressor discontinuation Posthoc subgroup analysis—significant reduction in time of vasopressor reduction in midodrine group |

Abbreviations: NICU, neonatal intensive care unit; MICU, medical intensive care unit; RCT, randomized controlled trial; SICU, surgical intensive care unit.

Midodrine exerts significantly less gastrointestinal effects, has minimal central nervous system side effects, and demonstrates excellent bioavailability after oral administration. These desirable pharmacological properties lead to midodrine's potential application for new indications. After oral administration, it causes modest increases in supine and standing blood pressures in a dose-dependent manner. Its common adverse effects are related to its α -agonist properties and include piloerection, pruritus, paraesthesia, and urinary retention. Such side effects are seen in less than 5% of cases. Supine hypertension in patients who are profoundly hypotensive in ICU and who have continuous blood pressure monitoring can be picked up and managed.^{16–18} It is rapidly and almost completely absorbed in healthy volunteers, achieving a maximum plasma concentration of about 10 to 50 $\mu\text{g/L}$ within 40 minutes. Midodrine undergoes enzymatic hydrolysis in the systemic circulation to release its pharmacologically active metabolite, desglymidodrine, of which peak plasma concentrations are reached about 1 hour after a single dose. Absolute bioavailability of midodrine is 93% for oral tablets and 90% for oral solution. Midodrine is cleared from plasma after 2 hours (elimination half-life of 30 minutes). It undergoes extensive metabolism, with only 2 to 4% of a single dose excreted unchanged. Midodrine and desglymidodrine are primarily renally excreted.¹⁸

Midodrine was the most evidence-based and the most widely used option among the available drugs. Several single-site observational studies described the use of midodrine **►Table 3**. Whitson et al, in his group of patients in medical ICU, found that with use of midodrine the ICU stay reduced approximately 2 days in the midodrine group compared to patients receiving only intravenous vasopressors. Similar findings are noted by Poveromo et al and Rizvi et al in their studies. Poveromo et al, in his group of 94 cases admitted in medical and surgical ICU, noted that after starting midodrine patients were weaned off intravenous vasopressors between 0.5 and 2.8 days and 96% of them remained free of vasopressors. Rizvi et al in his large series of surgical and medical ICU patients noted a significant reduc-

tion in median cumulative vasopressor dose and 48% were weaned off vasopressor within the first 24 hours. Levine et al in his prospective observational study found a 0.6 versus 2.2 μg reduction in intravenous vasopressor before and after starting midodrine. The most recent multicenter randomized trial from Santer et al published as the MIDAS trial has reported no significant reduction in the duration of intravenous vasopressor.¹⁹ However, various critics have pointed out that despite being a multicenter randomized controlled trial, the study took 8 years for completion suggesting selection bias as a significant shortcoming. While other published studies had titrated the dose of midodrine according to clinical response, Santer et al used fixed dose regimen for the study. This may have limited the therapeutic effect of midodrine much like using fixed-dose noradrenaline as a vasopressor.²⁰ The MIDAS trial found bradycardia in five patients; however, most of them remained asymptomatic like other trials that were although statistically significant didn't have any clinical significance. A posthoc subgroup analysis showed significant reduction in duration of intravenous vasopressor in patients who received epidural analgesia. This is similar to the effect caused by vasoplegia following traumatic spinal cord injury. This effect of midodrine on neurogenic vasoplegia and hence reduction in dependence of intravenous vasopressors was suggested for further study in the paper.^{21–24} In this study, we have noted that midodrine when administered and titrated between doses starting from 20 to 40 mg per day in divided doses maintains a stable MAP enabling weaning of intravenous vasopressors. The duration to completely wean off intravenous medications although varied between cases, the effect was seen within the first 24 to 48 hours of starting oral midodrine.

Limitations

The sample size is small. Although cervical spine injury is seen very frequently, patients requiring long-term inotrope support remains a small subgroup. Usually, these patients sustain high velocity injuries with multiple systemic injuries

precluding inclusion into the study. Many a times the mechanism of injury is also lethal. Also, the stringent public health restrictions taken to control the pandemic has reduced the number of high-velocity accidents.

Conclusion

The need for the study came as a direct outcome of the pandemic when critical care beds were in dire need. Isolated acute spinal cord injury after surgical stabilization remains in intensive care mainly for hemodynamic instability and for mechanical ventilation. In our observation, we found that the rate of reduction of intravenous vasopressors is similar to that found in literature. Although the sample size is small, this study shows clear benefit with the use of midodrine in weaning patients from intravenous vasopressor. Larger sample size with involvement of multiple centers dealing with spinal injuries will help in understanding the feasibility of this approach to rapidly wean intravenous vasopressor and its direct benefits in reducing ICU stay.

Ethical Approval

AIIMS Bhubaneswar Institute ethical committee. T/I-MF/21-22/21.

Funding

None.

Conflict of Interest

None declared.

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