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Double-blinded, placebo-controlled crossover trial to determine the effects of midodrine on blood pressure during cognitive testing in persons with SCI

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Abstract

Study design Clinical trial.

Objectives Individuals with spinal cord injury (SCI) above T6 experience impaired descending cortical control of the autonomic nervous system, which predisposes them to hypotension. However, treatment of hypotension is uncommon in the SCI population because there are few safe and effective pharmacological options available. The primary aim of this investigation was to test the efficacy of a single dose of midodrine (10 mg), compared with placebo, to increase and normalize systolic blood pressure (SBP) between 110 and 120 mmHg during cognitive testing in hypotensive individuals with SCI. Secondary aims were to determine the effects of midodrine on cerebral blood flow velocity (CBFv) and global cognitive function.

Setting United States clinical research laboratory.

Methods Forty-one healthy hypotensive individuals with chronic (≥ 1 -year post injury) SCI participated in this 2-day study. Seated SBP, CBFv, and cognitive performance were monitored before and after administration of identical encapsulated tablets, containing either midodrine or placebo.

Results Compared with placebo, midodrine increased SBP (4 ± 13 vs. 18 ± 24 mmHg, respectively; $p < 0.05$); however, responses varied widely with midodrine (-15.7 to $+68.6$ mmHg). Further, the proportion of SBP recordings within the normotensive range did not improve during cognitive testing with midodrine compared with placebo. Although higher SBP was associated with higher CBFv ($p = 0.02$), global cognitive function was not improved with midodrine.

Conclusions The findings indicate that midodrine increases SBP and may be beneficial in some hypotensive patients with SCI; however, large heterogeneity of responses to midodrine suggests careful monitoring of patients following administration.

Clinical trials registration NCT02307565.

Introduction

Focus on blood pressure in the medical literature is heavily skewed toward hypertension as opposed to hypotension. A recent PubMed search for hypertension yielded 490,320 literature references compared with 65,491 for hypotension over the course of the past century. Moreover, blood pressure threshold(s) used to define hypotension vary extensively, and whereas the diagnosis of hypertension is based solely on blood pressure, the diagnosis of hypotension is usually based on the presence of significant symptomatology reflecting cerebral hypoperfusion, which includes dizziness, light-headedness, pre-syncope and syncope, as well as nonspecific symptoms of generalized weakness, fatigue,

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nausea, cognitive slowing, blurry vision, leg buckling, or headache [1]. However, it should be appreciated that individuals with low blood pressure often remain asymptomatic and are, therefore, not diagnosed or treated. Further, long-standing sentiment argues that low blood pressure is a clinical syndrome unassociated with pathological consequences, and there persists an implicit belief that hypotension may convey significant cardiovascular benefit [2]. Yet 13-year all-cause and cardiovascular disease mortality risk was 2.4–3.4 times higher, respectively, in males 40–49 years with systolic hypotension compared with age-matched males with normal blood pressure [3], and in a recent meta-analysis all-cause mortality was 36% higher in association with orthostatic hypotension [4]. Moreover, there is a growing body of evidence that links persistent asymptomatic hypotension and orthostatic hypotension with adverse changes in health-related quality of life, as well as an increased incidence of anxiety and depression [2], cognitive deficits [5], hopelessness [5], and dementia [6, 7]. Therefore, treatment to increase and normalize low blood pressure, even in asymptomatic patients should be considered.

The loss of integral descending cortical control of autonomic cardiovascular regulation following spinal cord injury (SCI) results in a variety of measurable abnormalities in blood pressure, most prominently chronic hypotension, orthostatic hypotension, and autonomic dysreflexia. As in the general population, chronic hypotension and orthostatic hypotension in the SCI population are associated with cognitive deficits [8], adverse changes in health-related quality of life [9], increased arterial stiffness [10] and a 3–4-fold increased stroke risk [11]. Although evidence suggests improved cognitive performance following increases in blood pressure with midodrine [12], because most hypotensive individuals with SCI are asymptomatic there is a wide disparity between the incidence of hypotension and orthostatic hypotension and the diagnoses of these conditions and very few patients are treated for disorders of low blood pressure [13, 14]. In addition, there is a paucity of treatment options for hypotension and orthostatic hypotension that are clinically available and have been proven safe and effective for widespread use in the SCI population.

Nonpharmacological remedies for treatment of hypotension and orthostatic hypotension that are often prescribed in hypotensive individuals with SCI include: exercise [15], functional electrical stimulation [16], compression garments [17], and salt and water intake [18]; however, there is little supporting evidence for any of these interventions and the data that are available are of poor quality [19].

Pharmacological treatment options for hypotension and orthostatic hypotension include: midodrine hydrochloride [20], L-threo-3,4-dihydroxyphenylserine (droxidopa) [21], fludrocortisone and ergotamine [22], and ephedrine [23]. In a randomized, placebo-controlled, double-blinded clinical

trial in four individuals with SCI, midodrine (10 mg) increased average seated systolic blood pressure (SBP) to within a normotensive range (i.e., 110 and 120 mmHg), in one of the four subjects tested; one subject became hypertensive (average SBP of 143 mmHg) and two remained hypotensive (average SBP < 110 mmHg) [20]. Despite this limited evidence, midodrine is the most commonly prescribed anti-hypotensive agent used in the SCI population (<https://scireproject.com/evidence/rehabilitation-evidence/orthostatic-hypotension/>). Clearly, more data are needed to support the clinical management of hypotension and orthostatic hypotension in the SCI population.

The primary aim of this investigation was to test the efficacy of midodrine (10 mg), compared with placebo, to increase seated SBP at rest and during a battery of neuropsychological tests in hypotensive individuals with SCI in a randomized, double-blinded, crossover trial. Our primary hypothesis was that seated SBP would be significantly increased from baseline following midodrine administration as compared with placebo. Secondly, we hypothesized that the proportion and stability of SBP recordings within the normotensive range would be significantly increased during cognitive testing following administration of midodrine compared with placebo. Additional study aims were to determine if midodrine administration would be associated with increases in cerebral blood flow velocity (CBFv) and improved cognitive function compared with placebo. We hypothesized that CBFv would be significantly increased and that composite scores on a battery of cognitive tasks would be improved following midodrine administration.

Methods

Participants

This trial was conducted at two research facilities under identical study protocols, which were approved by the IRB committees at both facilities. Participants were deemed eligible for an in-person screening visit based on the following criteria: (1) between the ages of 18 and 65 years, (2) nonventilator dependent, (3) duration of injury more than 12 months, (4) native English speaker, and (5) better than 20/60 vision in worst eye with prescription eyewear. Exclusion criteria included: (1) three or more self-reported symptomatic episodes of autonomic dysreflexia per week, (2) current illness or infection, and (3) documented history of hypertension, diabetes, traumatic brain injury, or any neurological condition other than SCI.

Eligible participants underwent a screening visit to confirm that they met the World Health Organization definition of hypotension, (i.e., SBP ≤ 110 mmHg for males and ≤ 100 mmHg for females) [24]. At the screening visit blood

pressure was measured at 1-min intervals for 5-min in the seated and supine positions using manual auscultation at the brachial artery. Eligibility for inclusion in the study was based on either: (1) a supine SBP ≤ 90 mmHg; (2) seated SBP ≤ 110 mmHg for males or ≤ 100 mmHg for females, or (3) a fall in blood pressure $\geq 20/10$ mmHg within 5 min of assuming a seated upright position. Eligible participants were then scheduled for two testing visits and were issued a participant ID that was associated with the randomized order as either: midodrine/placebo or placebo/midodrine. The study participants, the research staff, and the investigators were blinded as to the order of administration and the randomization scheme was generated by the research pharmacist at the James J Peters VAMC who was responsible for dispensing the study medication. To limit the chance of autonomic dysreflexia during or after testing, we scheduled participant visits the day after their bowel-care routine and asked that they void their bladder immediately before testing began on each visit.

Procedures

Participants arrived at the testing site between 9 a.m. and 2 p.m. and remained in their wheelchair in the seated position for all study procedures, which were identical on both study visits. The two-study visits were scheduled no less than 2 and no more than 10 days apart and participants were asked to arrive at the laboratory at approximately the same time of day on both visits. Experiments were conducted in a quiet and temperature-controlled room and participants were instructed to avoid consuming caffeine, alcohol, and nicotine products for 12 h prior to testing. Vigorous unaccustomed exercise was also avoided for 24-h prior to testing. Participants were asked to empty their bladder upon arrival to the testing laboratory, to limit the influence of reflex sympathetic activation on peripheral vascular tone from bladder distension, and medications were stopped for ~ 5 half-lives (at the subject's primary care physicians' discretion) whenever possible. While resting quietly in the seated position, participants were instrumented with three electrocardiogram electrodes, finger, and brachial blood pressure monitors and a head harness to secure probe placement for transcranial Doppler ultrasound recording of CBFv. After instrumentation, a 5-min continuous baseline assessment of heart rate, blood pressure, and CBFv was recorded, while the participant rested quietly prior to administration of the initial neuropsychological battery of tests. After completion of the neuropsychological battery, midodrine or placebo was administered to the study participants in identical encapsulated tablets with a glass of water. Following administration of study medication participants rested quietly in their wheelchairs for 45-min. After which, and prior to beginning the second cognitive test battery, a 5-min continuous assessment of heart rate, blood pressure, and

CBFv was recorded. The second neuropsychological battery was then conducted and heart rate, blood pressure, and CBFv were monitored and recorded. The cognitive battery and hemodynamic monitoring occurred between 45 and ~ 90 min after dosing, which corresponds to peak blood pressure effects during a head-up tilt maneuver following administration of midodrine 10 mg. [25]

Heart rate and blood pressure

The electrocardiogram recording was performed using a bio-amplifier (Model RESP 1 with ECG: UFI, Morro Bay, CA, USA), with electrodes placed at the right and left mid-axillary lines in the 5th intercostal space and at the right anterior axillary line. Continuous beat-to-beat blood pressure (mmHg) was assessed at the finger using photoplethysmography (Finometer PRO, Finapres Medical Systems B. V., The Netherlands) and at 1-min intervals at the brachial artery with manual auscultation (Series Wall Mobile Sphygmomanometers, Trimline Medical Products, Raritan, NJ, USA). The beat-to-beat electrocardiogram and photoplethysmography blood pressure signals were sampled at 500 Hz and were continuously monitored in real time on a computer screen. The digitized signals were stored on a computer hard-drive for subsequent analysis using custom data analysis programs written with LabVIEW graphical software for instrumentation (National Instruments, 11500 North Mopac Expressway Austin, TX 78759-3504). Brachial artery blood pressure recordings were used to calibrate the finger blood pressure assessments, to determine the proportion of blood pressure recording within the normotensive range and to calculate the area-under-the-curve (AUC) of the blood pressure recordings during each of the cognitive batteries before and after administration of study drug. The normotensive range was defined as a SBP between 110 and 120 mmHg and a diastolic blood pressure between 70 and 80 mmHg.

Cerebral blood flow velocity

Transcranial Doppler ultrasound technology (Terumo Cardiovascular Systems 1311 Valencia Avenue Tustin, CA 92780-6447) was used to measure CBFv. The probe was operated at a frequency of 2.0 MHz to visualize the middle cerebral artery and insonation was through the left temporal window. The middle cerebral artery was identified by the target depth (45–55 mm), sound, and direction of flow (i.e., toward the probe), the characteristic spectral waveform and relatively faster flow velocity compared with surrounding cerebral vessels. Once the middle cerebral artery was visualized, probe placement was secured for the duration of testing using a head harness. Data output from the transcranial Doppler ultrasound was monitored in real time and

included systolic flow velocity, diastolic flow velocity, and mean flow velocities, which were recorded in centimeters per second (cm/s). The beat-to-beat signals were sampled at 500 Hz and were stored on a computer hard-drive for subsequent analysis using custom data analysis programs written with LabVIEW graphical software for instrumentation.

Neuropsychological testing

Participants underwent an abbreviated, nonmotor dependent, cognitive battery, to assess global cognitive function. This battery included tests of verbal fluency (Controlled Oral Word Fluency Test), verbal learning and memory (Hopkins Verbal Learning Test-Revised), cognitive inhibition (Stroop), auditory working memory (WAIS-IV Letter-Number Sequencing), cognitive flexibility (Oral Trail Making Test), and processing speed (Symbol Digit Modalities Test). The battery took about ~45 min to complete and was performed by the participants before and after administration of study medication on each study visit. A different version of each neuropsychological test was used at each time point to minimize a possible learning effect. Cognitive impairment was defined by a Global Deficit Score (GDS) of at least 0.5, which converts demographically-corrected *T*-scores to a deficit score, representing the distance each test score is below the normative mean [26]. Overall GDS is the average of all converted test scores and a GDS score of 0.5 or higher translates to performance of at least 1 SD below the normative mean on at least half of the cognitive measures. This methodology has demonstrated discriminative validity in detecting individuals with neurological disorders and cognitive impairment [27], as well as external validity with disease state and everyday functioning outcomes [28]. GDS was calculated under each of the four test conditions: pre- and post-placebo administration; pre- and post-midodrine administration.

Statistical analyses

Repeated measures ANOVA models were constructed to determine significant main and interaction effects for drug (midodrine and placebo) and time (pre- and post-administration) for the systemic and cerebral hemodynamics and for cognitive GDS. Because in these 2×2 models, the interaction effect is equivalent to a paired *t* test on the change scores [29], we also calculated effect sizes (Cohen's *d*) [30], 95% confidence intervals, Bayes factors and Bayesian credible intervals from the *t*-test calculations [31]. For the change scores, mean differences were calculated as midodrine minus placebo. Multilevel modeling using the lme4 package in R was used to determine the relationship between changes in SBP and changes in mean flow velocity

from pre- to post-testing following administration of midodrine compared with placebo.

To assess SBP stability, we used the serial brachial recordings and set the normotensive systolic range between 110 and 120 mmHg, inclusive. To quantify stability, for the time series of SBP values under each time and drug combination, we first calculated the percentage of beats that fell within the desirable range and then expanded the range serially by ± 10 mmHg, such that the subsequent systolic range was 100–130 mmHg, and repeated the percentage calculation until we were inclusive of all SBP observations (i.e., 40–190 mmHg). The resulting percentage within each range was then plotted against the SBP range at each iteration and the AUC was calculated for each plot. The same method was applied to the serial diastolic blood pressure data, with the desirable range set at 70–80 mmHg. The blood pressure processing and AUC calculations were performed with a custom LabVIEW program. The larger the AUC, the closer the systolic and diastolic blood pressure values were to the respective desirable range, and the more stable were the signals across the recording period. To assess the efficacy of midodrine to normalize blood pressure, the proportion of values that fell within the systolic and diastolic desirable ranges described above was also quantified. As with the hemodynamic data from above, the AUC and proportion in the desirable range data were analyzed with a drug \times time repeated measures ANOVA and change score analysis with paired *t* tests was used to calculate effect sizes, confidence intervals, Bayes factors and Bayesian credible intervals.

All continuous data are presented as mean \pm standard deviation and significance was set at an α of <0.05 . Statistical calculations were performed using SPSS and JASP (for the Bayesian calculations) and R for the multilevel modeling.

Results

Characteristics of the participants

A total of 43 individuals with SCI were consented to participate; however, two withdrew prior to initiation of the study procedures, therefore data are reported in 41 participants (Table 1). The participants were mostly male, with cervical (90%), motor-complete lesions (81%). Self-reported levels of physical activity suggested that most (85%) engaged in at least 1 day of exercise/week at a moderate intensity and that they were otherwise healthy. Twenty participants were randomly assigned to receive midodrine on the first study visit and placebo on the second visit and 21 received placebo first; there were no significant differences for hemodynamics by randomization order.

Table 1 Subject characteristics.

	Participants (<i>n</i> = 41)
Age (years)	44 ± 12
Males, <i>n</i> (%)	33 (80)
Caucasian, <i>n</i> (%)	23 (56)
African American, <i>n</i> (%)	8 (20)
Hispanic, <i>n</i> (%)	8 (20)
Other, <i>n</i> (%)	2 (5)
American Veteran, <i>n</i> (%)	6 (15)
BMI (kg/m ²)	24 ± 4
Duration of injury (years)	16 ± 12
Level of injury	C4-T9
AIS A, <i>n</i> (%)	18 (44)
AIS B, <i>n</i> (%)	15 (37)
AIS C, <i>n</i> (%)	6 (15)
AIS D, <i>n</i> (%)	2 (5)

Data are means ± SD; other ethnicity = 1 Asian and 1 East Indian.

BMI body mass index, *m* meters, *kg* kilograms.

Table 2 (a) Average pre-treatment hemodynamics. (b) Average post-treatment hemodynamics.

	Placebo	Midodrine
(a) Pre-treatment		
Heart rate (bpm)	68.0 ± 10.2	67.6 ± 10.9
Systolic BP (mmHg)	98.1 ± 14.0	98.6 ± 16.3
Diastolic BP (mmHg)	57.8 ± 9.5	59.6 ± 10.6
Systolic FV (cm/s)	69.4 ± 19.2	70.0 ± 15.9
Mean FV (cm/s)	43.3 ± 13.3	43.5 ± 10.7
Diastolic FV (cm/s)	30.4 ± 8.3	29.7 ± 7.8
(b) Post-treatment		
Heart rate (bpm)	65.0 ± 10.5	60.0 ± 12.0
Systolic BP (mmHg)	106.3 ± 18.0	115.0 ± 27.1
Diastolic BP (mmHg)	61.4 ± 13.3	66.0 ± 16.5
Systolic FV (cm/s)	70.5 ± 15.6	71.0 ± 16.8
Mean FV (cm/s)	44.6 ± 11.7	46.0 ± 10.5
Diastolic FV (cm/s)	31.3 ± 11.1	32.9 ± 13.2

Hemodynamic data collected during the 5-min of seared rest before and after treatment with placebo and midodrine. Data are means ± SD.

bpm beats per minute, *BP* blood pressure, *FV* flow velocity, *cm* centimeters, *s* seconds

Resting hemodynamic responses

Average systemic and cerebral hemodynamic data are presented for 5-min in the seated resting position prior to (Table 2a) and following (Table 2b) administration of study medication. Resting hemodynamics did not differ significantly prior to administration of study medication. The drug by time interaction effect was significant for heart rate

(all $p \leq 0.023$) (Fig. 1a) (95% CI of mean difference (midodrine minus placebo) = −10.1 to −3.8 bpm), SBP (Fig. 1b) (95% CI of mean difference = 9.0–24.1 mmHg), diastolic blood pressure (Fig. 1c) (2.5–10.4), mean flow velocity (Fig. 1e) (0.3–4.4 cm/s), and diastolic flow velocity (Fig. 1f) (0.4–5.4 cm/s), but was not significant for systolic flow velocity (Fig. 1d) (95% CI for mean difference = −3.3 to 6.8 cm/c). Results of the repeated measures ANOVA models are presented (Table 3), which indicate large Bayes Factors₁₀ (BF₁₀) for heart rate (BF₁₀ = 390.7), SBP (BF₁₀ = 319.1), and diastolic blood pressure (BF₁₀ = 15.0) indicating strong evidence that these hemodynamic responses to midodrine differed from placebo. Whereas the BF₁₀ for mean flow velocity (BF₁₀ = 2.01) and diastolic flow velocity (BF₁₀ = 1.84) were more modest and would be considered “anecdotal” evidence of a treatment effect [31].

The association between change in SBP and change in mean CBFv is depicted following placebo (Fig. 2a) and midodrine (Fig. 2b). Results of the multilevel modeling examining the relationship between SBP and mean CBFv indicate a significant main effect for SBP ($p = 0.02$); however, main effects for time ($p = 0.52$) and drug ($p = 0.34$) and the associated interaction effects were not significant (all $p > 0.31$). This suggests, that regardless of time or drug, higher SBP is associated with higher mean blood flow velocity in hypotensive individuals with SCI.

Nine of the 41 participants (22%) had an average resting SBP within the normotensive range following midodrine administration; however, SBP exceeded the normotensive range in 17 (41%) and remained below the desirable range in 15 (37%) participants (Fig. 3a). Further, the change in SBP (mmHg) following midodrine administration suggested wide variability (delta of −15.7 to +68.6 mmHg) in individual responses to the medication compared with placebo (delta of −15.8 to +38.7 mmHg) (Fig. 3b).

Normalization and stability of blood pressure

An average of 25 ± 4 brachial SBPs were collected in participants during each cognitive test battery. The interaction effects for the proportion of systolic or diastolic blood pressures within the desirable ranges were not significant (Table 3), indicating that treatment with midodrine did not “normalize” blood pressure compared with placebo. The AUC of blood pressure “stability” before and after administration of placebo and midodrine is also summarized (Table 3). The interaction effect for AUC was not significant for systolic or diastolic blood pressure, which indicates that the midodrine treatment did not improve blood pressure stability compared with placebo. Corresponding AUC curves for SBP are presented for three participants pre- and post-midodrine administration (Fig. 4); one participant who remained hypotensive (left panel), one

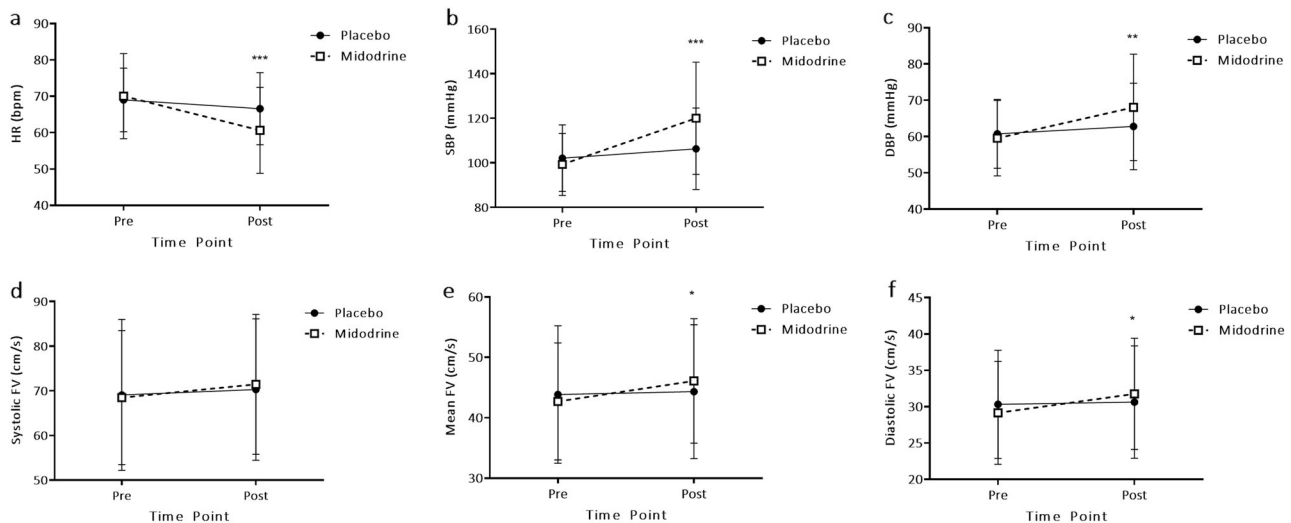


Fig. 1 Resting systemic and cerebral hemodynamic responses to placebo and midodrine. Results of the repeated measures ANOVA models for heart rate (a), systolic blood pressure (b), diastolic blood pressure (c), systolic flow velocity (d), mean flow velocity (e), and

diastolic flow velocity (f) pre- to post-placebo (closed circles) and midodrine (open squares) administration. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ for the drug by time interaction effect.

Table 3 Hemodynamic changes and blood pressure instability: midodrine vs. placebo.

Variable	p value	Mean Difference	95% CI of mean Difference	Bayes Factor ₁₀	Effect size	Effect size 95% credible interval
Heart rate (bpm)	<0.001	-7.0	-10.1 to -3.8	390.70	-0.93	-1.39 to -0.47
Systolic BP (mmHg)	<0.001	16.5	9.0-24.1	319.10	0.90	0.44-1.37
Diastolic BP (mmHg)	<0.001	6.4	2.5-10.4	15.00	0.66	0.21-1.12
Systolic FV (cm/s)	0.48	1.8	-3.3 to 6.8	0.21	0.13	-0.28 to 0.55
Mean FV (cm/s)	0.023	2.3	0.3-4.4	1.84	0.47	0.05-0.91
Diastolic FV (cm/s)	0.026	2.9	0.43-5.4	2.01	0.46	0.05-0.90
Systolic proportion in desirable range	0.86	-0.01	0.14-0.11	0.17	-0.04	-0.44 to 0.36
Systolic AUC (au)	0.76	159.4	-872.6 to 1191	0.18	0.06	-0.35 to 0.46
Systolic standard deviation (mmHg)	0.88	-0.2	-2.8 to 2.4	0.17	0.03	-0.43 to 0.37
Diastolic proportion in desirable range	0.16	-0.1	-0.22 to 0.04	0.44	0.28	0.13-0.70
Diastolic AUC (au)	0.13	-385.4	882.6-111.9	0.52	-0.30	-0.73 to 0.10
Diastolic standard deviation (mmHg)	0.48	-0.62	-2.40 to 1.15	0.21	-0.14	-0.55 to 0.26

Hemodynamics collected during the cognitive assessments following administration of midodrine compared with placebo.

p value = drug \times time interaction effect, which equals a paired t test comparing change scores of midodrine minus placebo.

Mean difference = average difference in change scores (post-test-pre-test) between midodrine minus placebo.

95% CI of mean = frequentist confidence interval about the mean difference in change score between midodrine minus placebo.

Bayes Factor₁₀ = the likelihood of the data under the alternate hypothesis vs the null hypothesis.

Bayes effect size = the median Bayesian effect size for the difference in change scores between midodrine minus placebo using an estimate, the population standard deviation as the denominator.

Bayes effect size 95% credible interval = the Bayesian credible interval about the median effect size.

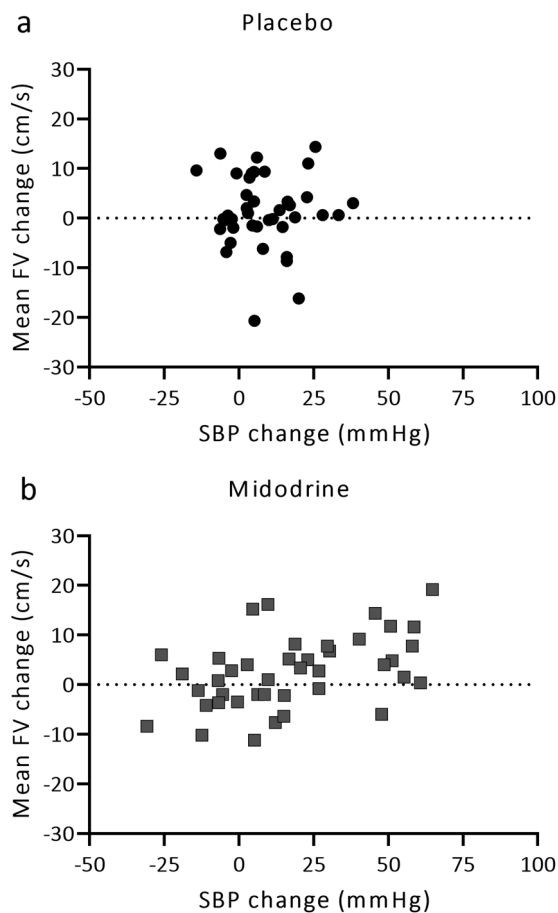


Fig. 2 Relationship between change in SBP and change in MFV. The relationship between change in systolic blood pressure (SBP) and mean cerebral blood flow velocity (FV) following administration of placebo (a) and midodrine (b).

participant who was normotensive (middle panel) and one participant who became hypertensive (right panel) after midodrine administration. Increased AUC (i.e., improved blood pressure stability within or near the desired range) was noted in the participant who had a normotensive response to midodrine (middle panel). Of note, midodrine was effective at stabilizing blood pressure within or near the normotensive range in 6 of the 41 study participants.

GDS analyses

Sixty-three percent of the study participants exhibited an average GDS ≥ 0.5 before administration of placebo or midodrine, indicating impaired function in more than half of the cognitive domains tested. There were no significant main or interaction effects for cognitive GDS (interaction $p = 0.91$, $BF_{10} = 0.17$), suggesting that compared with placebo, midodrine administration did not improve global cognitive function in these 41 hypotensive participants with SCI. However, it might be noted that of the nine participants with a normal SBP following midodrine, three

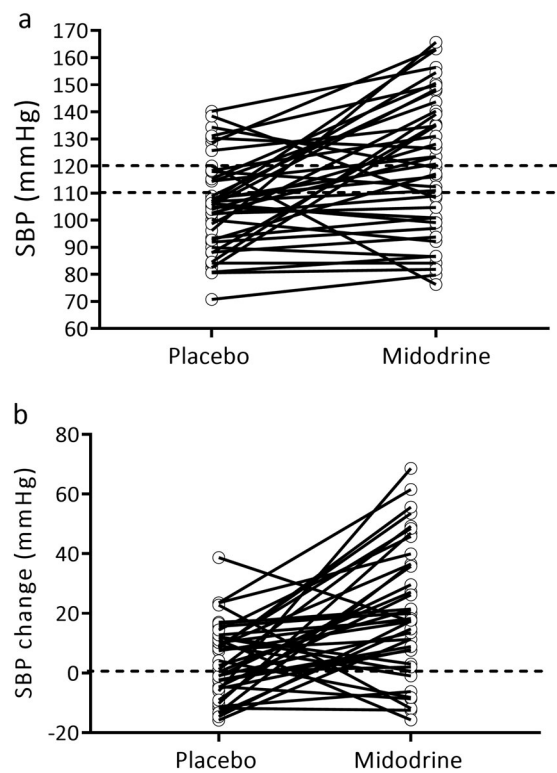


Fig. 3 Systolic blood pressure following placebo and midodrine. Average (a) and the change (b) in 5-min seated resting systolic blood pressure (mmHg) following administration of placebo and midodrine for each participant. The dashed lines represent the upper and lower limits of the normotensive range (a) and the no change (b).

showed evidence of improved global cognitive function after administration.

Discussion

Hypotension and orthostatic hypotension are not high on the clinical priority list in patients with SCI, which is due in part to the lack of safe and effective treatment options available for use in the population [19]. Yet low resting blood pressure and orthostatic hypotension may be clinically relevant signs to indicate impaired autonomic nervous system control of cardiovascular function and are associated with significant adverse health outcomes. Therefore, treatment of hypotension and orthostatic hypotension should be considered important aspects in the clinical management of individuals with SCI. It was our goal to determine the effectiveness of midodrine, compared with placebo, to increase and maintain SBP within a tight normotensive range of 110–120 mmHg in hypotensive participants with SCI. Our findings suggest that, although midodrine did increase blood pressure, large heterogeneity of response was evident such that only a small percentage (22%) of the study participants had SBPs within the normal range following administration. Furthermore, the

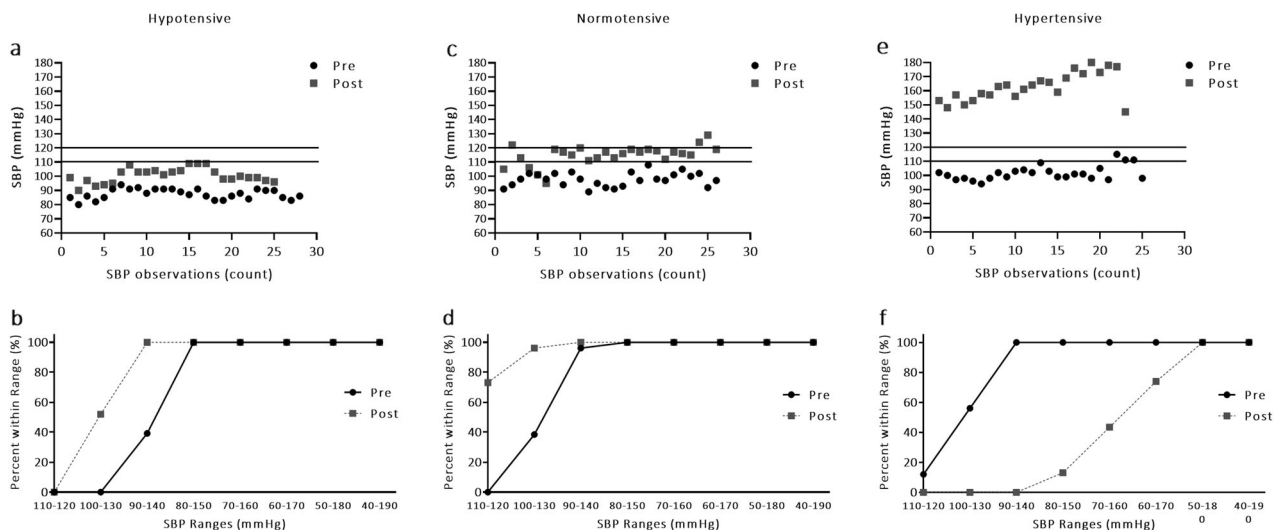


Fig. 4 Stability of systolic blood pressure during cognitive testing before and after midodrine. Systolic blood pressures pre- (closed circles) and post- (open squares) midodrine administration in 3 individual participants (top) and the AUC curves which were generated from these data (bottom). Left panel: the participant is hypotensive pre- and post-midodrine administration (a) and the AUC indicates a modest improvement in normalizing systolic blood pressure post-

midodrine administration (b). Middle panel: the participant is hypotensive pre-midodrine and normotensive post-midodrine administration (c) and the AUC reflects an increased proportion of normal blood pressure post-midodrine administration (d). Right panel: the participant is hypotensive pre-midodrine and hypertensive post-midodrine administration (e) and the AUC reflects a reduced proportion of normal blood pressure post-midodrine administration (f).

proportion and the stability of SBPs recordings within the normotensive range were not improved with midodrine compared with placebo.

There is substantial evidence that demonstrates improved standing blood pressures and reduced symptoms associated with cerebral hypoperfusion following midodrine administration in models of symptomatic neurogenic orthostatic hypotension [32]; however, there is limited evidence to support widespread utility in the SCI population. While it is not our intent to discourage the use of midodrine to treat hypotension and orthostatic hypotension in the SCI population, we sought to (1) increase awareness of the heterogeneity of response, (2) encourage more frequent monitoring of blood pressure following prescription, and (3) adjust dose as needed. With that in mind, several points should be considered when interpreting these results in the context of clinical algorithms used to manage hypotension and orthostatic hypotension in the SCI population: (1) lack of a clear consensus regarding the definition of hypotension and normotension, (2) changing guidelines for the management of hypertension, (3) highly prevalent blood pressure instability, and (4) the impact of anti-hypertensive treatment on blood pressure surges during autonomic dysreflexia.

There is a lack of clarity regarding the definition of hypotension that contributes to low diagnosis and treatment rates. A recent systematic literature search, that included 63 publications involving over 7000 participants, found 15 different definitions for hypotension [33], and different definitions yielded significantly altered incidence rates [34].

Large epidemiological studies tend to define hypotension as the lowest 5–30% of the population [2, 35] while smaller prospective studies use upper limit cutoffs of between 100 and 120 mmHg systole [36]. The definition of hypotension in the SCI population as published in the *International Standards to Document Remaining Autonomic Function after Spinal Cord Injury* is a supine SBP < 90 mmHg. [37] However, the World Health Organization defined hypotension as a resting SBP of <110 mmHg for males and <100 mmHg for females without regard to diastolic blood pressure [24], which has been used by our group to define hypotension in persons with chronic SCI [8].

The diagnosis of hypotension is usually based on the presence of significant symptomology. Despite views that, in the absence of clinical symptomology, hypotension represents a “non-disease” state [38], recent evidence suggests that lower baseline SBP predicts incident depression at a 2-year follow-up after adjustment for socioeconomic status and relevant clinical factors (cardiovascular disease, chronic illness, and frailty) [39]. In addition, individuals between the age of 30 and 75 years with asymptomatic hypotension are at increased risk for cognitive and affective disorders, including decreased memory and concentration [5], higher rates of hopelessness [5], and an increased prevalence of dementia, which includes both Alzheimer’s disease and vascular dementia [7]. Therefore, the treatment of asymptomatic hypotension in the SCI population should be considered a clinical priority.

To our knowledge there are no long-term studies documenting the potential association between hypotension and

incident depression or cognitive changes with aging in the SCI population. However, we previously documented higher rates of depressive symptom reporting and deficits in memory and information processing in hypotensive individuals with SCI compared with a normotensive SCI cohort [8]. Moreover, although most hypotensive individuals with SCI do not spontaneously report symptoms, when asked directly, they are able to ascribe adverse impacts of hypotension and orthostatic hypotension on their activities of daily living and quality of life [9]. Although the results herein do not demonstrate a lessening of cognitive dysfunction following increases in blood pressure with midodrine, the data do suggest that higher blood pressures are associated with higher cerebral blood flow velocities and one-third of participants with normal SBP responses to midodrine displayed improved cognitive function. These results suggest that, if higher—more normal blood pressure is maintained with prolonged anti-hypotensive treatment, improvement in long-term cognitive performance may be evident.

There are nearly 200 prescription medications with FDA approval for label and off-label use to treat hypertension, and many patients require combinatorial therapy to maintain optimal blood pressure control. A similar approach to the treatment of hypotension and orthostatic hypotension may be beneficial; however, until a variety of safe and effective agents with different mechanisms of actions are identified, clinical treatment will be inadequate, and individuals will remain un- or under-treated. Further, while prioritizing the treatment of asymptomatic hypertension in clinical practice is well appreciated, lack of acknowledgment that there may be a blood pressure value that is recognized to be too low is noteworthy. Current guidelines used in treatment algorithms for hypertension indicate a normal SBP of <120 mmHg, with systolic pressures between 120 and 129 mmHg being elevated [40], therefore, we chose a desirable range for SBP of between 110 and 120 mmHg in this trial. Notwithstanding the lack of clear consensus regarding what constitutes normal blood pressure and the relatively tight normotensive range selected, it is not surprising that we document limited efficacy of midodrine to “normalize” blood pressure following a single 10 mg dose. However, what was surprising is the wide variability in response to midodrine, compared with placebo, in our participants with SCI.

We appreciate that blood pressure instability, which is commonly reported in persons with SCI [41], complicates the clinical management of hypotension and orthostatic hypotension. We recently noted that fluctuations in SBP of ≥ 20 mmHg, over a 30-day period were increased with age and duration of injury [42], which may be associated with the loss of baroreceptor buffering of blood pressure, similar to the general population [43]; therefore, management of

hypotension in the SCI population should aim to stabilize, as well as to normalize, blood pressure.

The AUC analyses suggest that the stability of the blood pressure, relative to the normotensive range, was not improved with midodrine. In fact, the AUC was lower following midodrine administration compared with following placebo in half of the participants. This finding indicates increased blood pressure instability following midodrine administration, which speaks to the large heterogeneity of responses. However, it should be noted that a few participants did respond to midodrine with a normal and stable SBP, as depicted in Fig. 3c, d. Average brachial SBP was within the normotensive range in 9 of the 41 participants tested and these participants tended to be younger and injured fewer years than those with inadequate and excessive responses to midodrine.

Given the heterogeneity of response to midodrine and significant blood pressure instability in persons with SCI, increasing the armamentarium of safe and effective clinical strategies is vitally important, particularly in individuals who are prone to autonomic dysreflexia. We did not induce autonomic dysreflexia in this trial and none of the participants reported feeling symptomatic prior to or after administration of study drug. A previous study found that increases in blood pressure during penile vibrator stimulation for sperm retrieval (i.e., a procedure known to induce autonomic dysreflexia) were not worsened with the addition of midodrine [44]. However, this response to midodrine was reported during a closely observed clinical procedure; home use of midodrine during life events that may induce autonomic dysreflexia should be studied. Additionally, the practice of “boosting” during athletic competition, should serve as an indicator of the importance of increasing blood pressure—safely—to avoid this dangerous and uncontrolled practice in athletes with SCI.

Limitations

There are several study limitations to consider when interpreting the findings reported. Based on prior evidence, we only tested the efficacy of a single 10 mg dose of midodrine, compared with placebo, over a relatively brief observation period; however, higher doses for those who remained hypotensive and lower doses for those in whom blood pressure was elevated above the normotensive range should be tested for efficacy. In addition, while the 10 mg dose did not improve blood pressure stability, a lower dose (2.5 or 5 mg) administered more frequently throughout the day may be more effective and may provide more clinically relevant information. We did not assess supine blood pressure responses to midodrine and did not investigate the effects on blood pressure during autonomic dysreflexia. We did not record symptom reporting in association with the increase in

blood pressure, which in many participants met the definition of autonomic dysreflexia (i.e., systolic increase >20 mmHg). The range selected to define normotension was narrow and arbitrary, because there are currently no guidelines, other than those which define elevated blood pressure and hypertension. Finally, the study sample included a largely homogeneous cohort of participants and extrapolation to the broader SCI population may be inappropriate.

Conclusion

Compared with placebo, midodrine, on average, significantly increased SBP; however, large heterogeneity of responses among these hypotensive participants with SCI were evident. Furthermore, and perhaps more concerning, was that midodrine appeared to increase blood pressure instability in about half of the participants tested. That said, prescription of midodrine may benefit individual patients, particularly those who are younger and injured for fewer years; this finding requires further study to definitively identify responders from non-responders. In addition, higher SBPs were associated with higher cerebral blood flow velocities, which may have beneficial effects on long-term cognitive function. Given the growing body of evidence indicating significant adverse sequela of untreated asymptomatic hypotension and orthostatic hypotension, identifying an armamentarium of safe and effective treatment options for use in the SCI population is needed.

Data availability

The data sets generated and analyzed in the current study are available from the corresponding authors upon request.

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Author contributions JMW oversaw and was primarily responsible for designing the study, participant enrollment, data collection procedures, database management, data analysis, result dissemination, and regulation compliance; JPW was primarily responsible for designing the study, data analysis, and result dissemination; CGK was primarily responsible for participant enrollment, data collection procedures, database management, and regulation compliance; NDC oversaw study design pertaining to the cognitive outcomes and was primarily

responsible for the cognitive data analyses; SCK was responsible for monitoring patient safety at the Kessler Foundation; TAD was responsible for participant enrollment and monitoring patient safety at the Kessler Foundation; EW was responsible for analysis of the cognitive outcomes; WAB monitored patient safety at the VA and oversaw data analysis and result dissemination.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics The authors certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

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