

Dose Response to the Norepinephrine Precursor Droxidopa in Hypotensive Individuals with Spinal Cord Injury

a) Specific Aims

Interruption of sympathetic cardiovascular autonomic regulation following spinal cord injury (SCI) is associated with significantly reduced plasma norepinephrine (NE) levels, hypotension and orthostatic hypotension (OH), particularly in individuals with high cord lesions. [1-4] Although the incidence of hypotension is reported to be as high as 70% in persons with cervical lesions (i.e., tetraplegia), the vast majority of these individuals remains asymptomatic and, therefore, does not raise clinical concern, or prompt intervention [5, 6]. While it is appreciated that clinicians are faced with substantial challenges in managing blood pressure (BP) in persons with SCI, contrary to the prevailing belief, asymptomatic hypotension and OH are not benign conditions. Reports suggest that asymptomatic hypotensive individuals with SCI may have subclinical cognitive dysfunction affecting memory and attention processing [7-11] and increased incidence of fatigue and depression compared to normotensive individuals with SCI. [7] It must be appreciated that to date, there are no FDA approved pharmaceutical options proven to be safe and effective for treatment of hypotension and OH in the SCI population. Until 2014, midodrine hydrochloride was the only agent with FDA approval for treatment of *symptomatic* neurogenic OH (NOH). Midodrine, an alpha-agonist, is the most commonly prescribed agent used to treat symptomatic hypotension in the SCI population despite a lack of convincing evidence of safety or efficacy. [12] In 2014 droxidopa (L-threo-3,4-dihydroxyphenylserine - NORTHERA; Chelsea Therapeutics, Charlotte, NC) was approved by the FDA for treatment of *symptomatic* NOH based on data collected in conditions of autonomic dysfunction. Droxidopa is a NE precursor that is stored in neuronal and non-neuronal tissue and has been shown to increase standing BP and reduce symptoms of orthostatic intolerance in individuals with symptomatic NOH. [13-15] We recently reported preliminary evidence of a mean increase in seated BP in individuals with SCI following oral administration of 400 mg of droxidopa; however, this dose was effective in only 5 of the 10 subjects tested and the BP effect waned over a 4-hour observation. [16] Because of its unique pharmacokinetic profile, [17] droxidopa is a highly promising agent to treat hypotension in persons with SCI. As such; there exists a pressing imperative to determine the clinical value and safety of droxidopa in hypotensive individuals with SCI.

Primary Aim 1.1: Dose optimization, open-label trial to determine the proportion of subjects with SCI with a normotensive response to droxidopa (**Efficacy #1**). Normotension will be defined as an average systolic BP (SBP) recorded 60-120 minutes after dose administration of 111-139 mmHg in males and 101-139 mmHg in females or a maximum dose of 800 mg is reached without adequate SBP response.

Primary Aim 1.2: Dose optimization, open-label trial to determine the proportion of subjects with SCI with a hypertensive response to droxidopa (**Safety #1**). Hypertension will be defined as a sustained elevation (≥ 30 consecutive minutes) in seated SBP $\geq 140/100$ mmHg or intolerable side effects considered related to study medication.

Secondary Aims: To determine the effect of the individualized optimal dose of droxidopa, compared to placebo, on (1) supine BP (**Safety #2**), (2) SBP during a head-up tilt (HUT)

maneuver to 70° (**Efficacy #2**) and change in cerebral blood flow velocity (CBFv) from supine to HUT (**Efficacy #3**).

b) Significance

Asymptomatic hypotension and OH are not benign conditions. Current reports suggest that hypotensive individuals with SCI perform significantly more poorly on cognitive tasks and that elevation in BP improves test performance in these individuals. [7-11] Additionally, we note increased self-reported incidence of fatigue, trouble with concentration and depression in hypotensive individuals with SCI [7, 10, 11] and report that these individuals are able to ascribe negative health related quality of life outcomes in association with BP dysregulation. [18] Although there is mounting evidence suggesting adverse consequences in association with asymptomatic hypotension and OH in the SCI population, clinical appreciation of these associations is lacking, [18] and we recently documented a nearly 40% prevalence of hypotension in veterans with SCI, based on clinical data entered into the medical record, whereas diagnosis and treatment were found in less than 1% of the population. [5, 6] While many individuals with SCI above T6 are chronically hypotensive, many also suffer with autonomic dysreflexia (AD), which is a potentially life threatening, [19] unpredictable and often silent elevation in BP that justifiably restrains clinical intervention to treat hypotension in these individuals. However, the normalization of BP is not synonymous with hypertension, and evidence regarding the effects of anti-hypotensive treatment on the BP response to ejaculation (i.e., AD provocation) did not differ from a no-drug condition. [20] Diminished clinical intervention to treat asymptomatic hypotension and OH is also a reflection of the lack of anti-hypotensive agents that have been rigorously tested and have been proven to be safe and effective for wide spread use in the SCI population. In fact, there are no pharmaceutical agents approved by the FDA for use to treat asymptomatic hypotension in any population, let alone the SCI population. There are presently two FDA agents that have been approved for use to treat *symptomatic neurogenic orthostatic hypotension* (i.e., dizziness with standing); midodrine and droxidopa, and neither agent has been adequately tested for use in asymptomatic hypotensive individuals with SCI. Both midodrine and droxidopa have been used to effectively treat symptomatic hypotension and OH in individuals with acute SCI as documented in several case reports, and there is preliminary evidence to support increases in seated BP following oral administration of these agents compared to placebo in open label trials. [16, 21-26] Based on limited evidence, midodrine is the most commonly prescribed anti-hypotensive agent in the SCI population, [12] however, our preliminary data (Figure 2) testing midodrine (10 mg) in a single-dose, randomized, placebo-controlled, double-blinded trial indicate seated hypertension (SBP ≥ 140 mmHg) in one-third of the subjects tested with another one-third remaining hypotensive. Droxidopa offers a promising alternative pharmaceutical option for treatment of hypotension and OH in persons with SCI, but due to limited critical evidence demonstrating safety and efficacy, this medication is not presently a viable clinical option.

c) Background and Preliminary Results

Asymptomatic Hypotension, OH & Related Outcomes:

As early as 1927 individuals with low BP were described as those who lacked stamina, tired easily, complained of cold extremities and showed an inability to do prolonged mental or physical work. [27] However, nearly a century later, the notion that hypotension may be a clinical concern has yet to gain substantial traction. In fact, several articles have challenged the notion that low BP is a health concern, suggesting that hypotension is the ideal “normal” BP and a benefit to longevity and cardiovascular health.[28, 29] We understand that the diagnosis and treatment of disease is usually based on causal associations between symptoms and physiological pathology; [30] but the “non-disease state” has been described as the diagnosis of a particular disease when confirmatory ‘symptomology’ is not readily apparent, [31] as in the

case of low BP. [30] It must be appreciated however, that the diagnosis and treatment of high BP and hypertension are readily made, regardless of symptomology, and we noted that although only 15% of veterans with tetraplegia had clinical values entered into the medical record reflecting hypertension, 39% were diagnosed with hypertension and 54% were prescribed at least 1 anti-hypertensive medication. [6] In contrast, the diagnosis and treatment of hypotension and OH are almost exclusively made based on the presence of significant symptomology, including: orthostatic dizziness, light-headedness, pre-syncope and syncope, as well as non-specific symptoms of generalized weakness, fatigue, nausea, cognitive slowing, blurry vision, leg buckling or headache. Whereas 39% of veterans with tetraplegia had clinical values entered into the medical record reflecting hypotension, less than 1% were diagnosed or treated for the condition. [6]

In the 1990's the British Journal of Medicine published a series of articles describing the association between low BP and mood disorders in the general population. [32-35] The findings suggest that, compared to normotensive individuals, otherwise healthy individuals with chronic hypotension report significantly increased incidence of depression, [32, 36-42] anxiety, [37, 38] unexplained tiredness, [32, 33] and poor perception of wellbeing.[34] It should be noted that because these associations were made in large epidemiological studies the clinical implication has met with skepticism. [43] With that appreciation, another report, which aimed to determine the influence of high BP on depression and anxiety found an inverse relationship, suggesting that low BP may confer greater risk. [44] Significantly increased rates of depression and anxiety have been repeatedly reported in the SCI population. [45-47] We recently documented an increased rate of self-reported fatigue and trouble concentrating in veterans with asymptomatic OH, [48] and found significantly increased Becks Depression Index in hypotensive individuals with SCI compared to the normotensive SCI cohort. [7]

Emerging evidence suggests that hypotension and OH may be associated with progressive cognitive decline with advancing age [49]. Cross-sectional analysis of more than 3000 participants in the Honolulu-Asia Aging Study found poorer cognitive performance in individuals with SBP < 110 mmHg compared to those with normal and high BP [50]. Cognitive deficits associated with chronic asymptomatic hypotension include: slowed cognitive speed, fewer word recall, decreased accuracy of response, limited attention, prolonged reaction times and reduced memory and concentration capacity [51-53]. In addition, several investigations have documented a link between asymptomatic OH and cognitive deficits [54-57], and poor test performance on tasks of recent recall and sustained attention and processing speed was evident in middle-aged subjects with asymptomatic OH compared to subjects without OH after adjustment for age [58]. The proposed association between hypotension, OH and cognitive deficits relates to chronic cerebral hypoperfusion and significantly reduced CBFv has been reported in otherwise healthy asymptomatic hypotensive subjects compared to age-matched normotensive subjects [52]. Further, Laboratory evidence suggests that elevation in BP improves CBFv and cognitive performance in healthy subjects, in post-acute stroke patients and in subjects with SCI. [8, 9, 59-61] We recently demonstrated a direct association between increases in BP and increased CBFv, [62, 63] and note a relationship between CBFv and cognitive performance in persons with SCI. [10, 11]

Operational Definitions:

There is a general lack of consensus regarding the definition of hypotension, as well as whether chronic hypotension exists, [64] or is a problem. [30, 65] In 1978, the World Health Organization (WHO) defined hypotension as a SBP \leq 110 mmHg for males and \leq 100 mmHg for females, without regard to diastolic BP (DBP).[66] However, much of the literature on hypotension is equivocal regarding the definition. Large epidemiological studies discuss

hypotension as a BP in the lowest 5-30% of the population, [37, 38, 40] while smaller studies report cut-offs to define systolic hypotension of between 100 and 120 mmHg. [32-35, 39] In addition, there is discussion about whether or not “constitutional hypotension” exists, [64] and while several Eastern European countries diagnose and treat individuals with hypotension, many English speaking countries are not convinced that low BP is a clinical syndrome, and actually believe that hypotension conveys significant cardiovascular benefit. [28] Yet, compared to normotensive males, 13-year mortality risk for all causes and cardiovascular disease was 2.4 to 3.4 times greater, respectively, in men ages 40-49 with systolic hypotension; by comparison, systolic hypertension conveyed a 1.7 fold increase in all-cause mortality. [67]

Unlike hypotension there is a clear definition of OH, which was first established in 1996 by the American Autonomic Society and the American Academy of Neurology as a fall in BP of $\geq 20/10$ mmHg, regardless of symptoms. [68] In fact, dissociation between the fall in BP reflective of OH and orthostatic dizziness has been reported. [69-71] Regardless of symptoms, however, several large epidemiologic studies report associations between OH and increased hospitalizations, [72] incidence of ischemic stroke [73] and coronary heart disease risk [74] and higher mortality in the elderly subjects after controlling for confounding factors. [71, 75, 76] While the predominance of information on OH and mortality has been reported in elderly cohorts, several investigators have demonstrated significantly poorer prognosis among younger individuals (early to mid-40s) who were OH positive compared to OH negative. [70, 74, 77] Of note, these individuals were otherwise healthy and remained asymptomatic during episodes of OH, and therefore, did not raise clinical concern. [70, 77]

Asymptomatic Hypotension & OH in the SCI Population:

Due to de-centralized autonomic cardiovascular control and low plasma NE, persons with SCI struggle with circadian BP dysregulation, [78-80] and individuals with spinal cord lesions above T5 tend to be persistently hypotensive [79-84] with frequent episodes of OH. [1, 85-88] Although many of these individuals remain asymptomatic [89-91], mounting evidence suggests adverse cardiac, [92, 93] cerebral [10, 11, 94] and cognitive consequences. [7] Further, it has been suggested that the superimposition of hypotension and cognitive impairment on the physical, social and emotional limitations already experienced by many individuals with SCI can adversely impact autonomy, social independence and quality of life (QOL) [18, 95, 96]. While we appreciate that the asymptomatic nature of hypotension and OH often precludes clinical intervention, wide and frequent fluctuations in BP also pose a significant impediment to effective treatment in the SCI population.

Individuals with high cord lesions paradoxically struggle with chronic hypotension and OH as well as significant life threatening and unpredictable increases in BP during episodes of AD. [97, 98] Further, although AD may be associated with symptoms such as headache, pounding in the ears and head, sweating below the lesion level, silent AD has been reported and can lead to cerebral hemorrhage [99, 100] and even death. [19, 101] The lack of rigorous clinical trials aimed at identifying the impact of anti-hypotensive treatment on BP increases during AD warrants restraint in treatment to normalize BP in the SCI population. However, increases in BP with midodrine during sexual stimulation to promote ejaculation, did not significantly heighten the BP response compared to no-drug. [20] Midodrine is the only anti-hypotensive agent that has been tested on the BP response to AD, which is an alpha-agonist that binds to vascular alpha receptors causing vasoconstriction and increased BP. Because of direct alpha receptor binding, midodrine may, if tested more rigorously, increase BP during a bout with AD. In contrast, droxidopa is a prodrug that is converted to NE, stored primarily in non-neuronal tissue and is released upon stimulation of the post-ganglionic sympathetic neurons during an

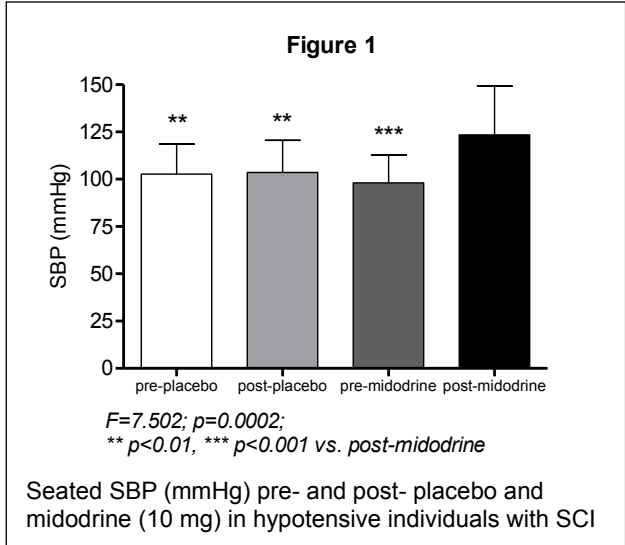
orthostatic provocation. [17] Because droxidopa is a prodrug and is not bound to the alpha receptors, exacerbation of the BP elevations during AD seems less likely, but this has not been tested.

Anti-Hypotensive Treatment in SCI:

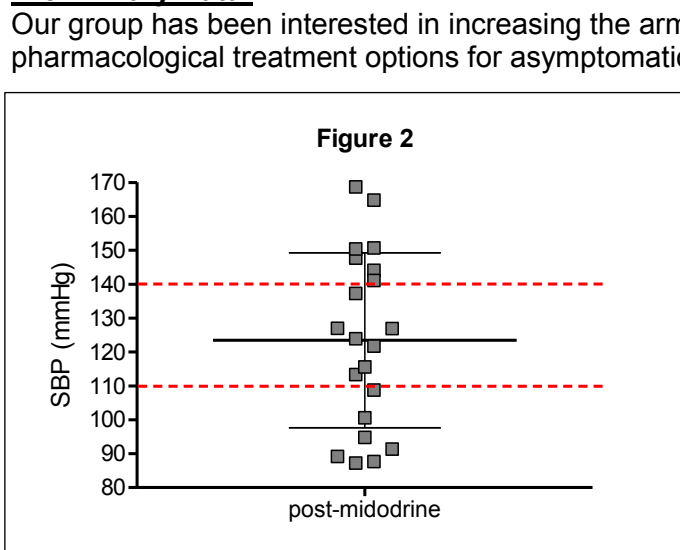
Midodrine hydrochloride is the most commonly prescribed anti-hypotensive agent in the SCI population, although its clinical utility has not been adequately determined. [12] Available data describing the effects of midodrine on BP in the SCI population include three case reports, [21, 22, 102] one randomized placebo-controlled trial in 4 individuals with tetraplegia, [24] a dose titration, open label trial, in 10 individuals with tetraplegia [25] and two head-to-head comparisons describing the effects of midodrine and the nitric oxide synthase inhibitor, L-arginine-N-methyl-ester (L-NAME) on BP and CBFv. [62, 63] The three case studies report significant attenuation in the symptoms of syncope in newly injured individuals with SCI, [21, 22, 102] and the two laboratory assessments provide preliminary evidence on the efficacy of midodrine to raise BP. Nieshoff et al. reported increased seated SBP following 10 mg midodrine in 3 of the 4 individuals tested; however, only 2 of the 4 individuals experienced improved exercise performance. [24] More recently our group has reported a significant increase in orthostatic BP following administration of midodrine (10 mg) compared to a no-drug condition. [25] However orthostatic BP responses to midodrine varied greatly (+37 to -11 mmHg) and supine hypertension was noted in 4 of the 10 subjects. [25] While mean orthostatic SBP was comparable following midodrine (110±24 mmHg) and L-NAME (110±26 mmHg), 5 individuals remained hypotensive with midodrine compared with only 2 individuals following L-NAME administration, [63] and we report direct association between increased in BP and increases in CBFv during HUT and cognitive testing in these individuals. [62, 63] Although we report promising data describing the safety and efficacy of L-NAME (1 mg/kg) on supine [4, 103] and orthostatic BP [104], L-NAME is administered intravenously, and is not readily available for clinical use. There is evidence that acetylcholinesterase inhibition (AChI) improves orthostatic tolerance in individuals with NOH, [105-108] and we reported the effects of AChI with pyridostigmine bromide (60 mg) on orthostatic BP responses in hypotensive individuals with SCI. [109] While the efficacy of pyridostigmine to increase orthostatic BP relative to a no-drug condition was not astounding, HUT duration was extended with AChI in 2 individuals with pre-syncope symptoms during the no-drug trial. [109]

In 2014 the FDA approved droxidopa for treatment of orthostatic dizziness, light-headedness, or the “feeling that you are about to black out” in adults with symptomatic NOH caused by primary autonomic failure. Droxidopa is a synthetic amino acid that is converted to NE in both neuronal and non-neuronal tissue. [17] Data on the safety and efficacy of droxidopa has been reported in patients with NOH stemming from conditions of Parkinson’s Disease (Pkd), pure autonomic failure (PAF), multiple system atrophy (MSA) and diabetic neuropathy. [13, 14, 110-118] The effective dose of droxidopa which increases standing BP in persons with NOH ranges from 200 mg to 2000 mg/day, and doses are generally administered TID. [110, 111, 119] Although the effective dose of droxidopa was greater in individuals with MSA (1327±133 mg) compared to those with PAF (875±230 mg), resulting in significantly increased plasma NE concentrations in the MSA group, comparable pressor effects were noted, [15, 110] suggesting that conversion to NE occurs predominately in non-neuronal tissue. [17] This is an important distinction, which holds promise for the use of droxidopa to treat hypotension and OH in the SCI population because decentralized post-ganglionic sympathetic nerves results in markedly reduced plasma NE levels and lack of a coordinated release of NE during orthostatic provocation. To date there are only 3 reports which document findings on the effects of droxidopa to treat hypotension and OH in the SCI population: 1) a case report in a 72 year-old female with a compressed cord at T4 [26], 2) a case report in a 65 year-old male with acute C4

traumatic SCI [23] and 3) an open-label dose escalation trial in 10 individuals with chronic SCI (C3-T10). [16] In the first case report droxidopa (600 mg) was associated with a 10-fold increase in plasma NE, an attenuated fall in orthostatic BP and marked reduction in symptoms of orthostatic intolerance. [26] In the second case report droxidopa (300 mg BID) was associated with an attenuated fall in seated BP and improved symptoms of orthostatic intolerance. [23] It should be noted that BP was not normalized in these two case reports, but subjects reported less symptomatic OH. Results from the dose escalation trial suggest that a single dose of droxidopa (400 mg) normalized seated SBP in 5 of the 10 subjects tested, with limited evidence of supine or seated hypertension; however, the BP response to droxidopa waned over time and by 4-hours post-drug BP was not significantly different from pre-drug levels. [16] These reports highlight the need for a more thorough investigation of dose effectiveness for achieving adequate orthostatic BP control, prior to wide spread use in the SCI population.



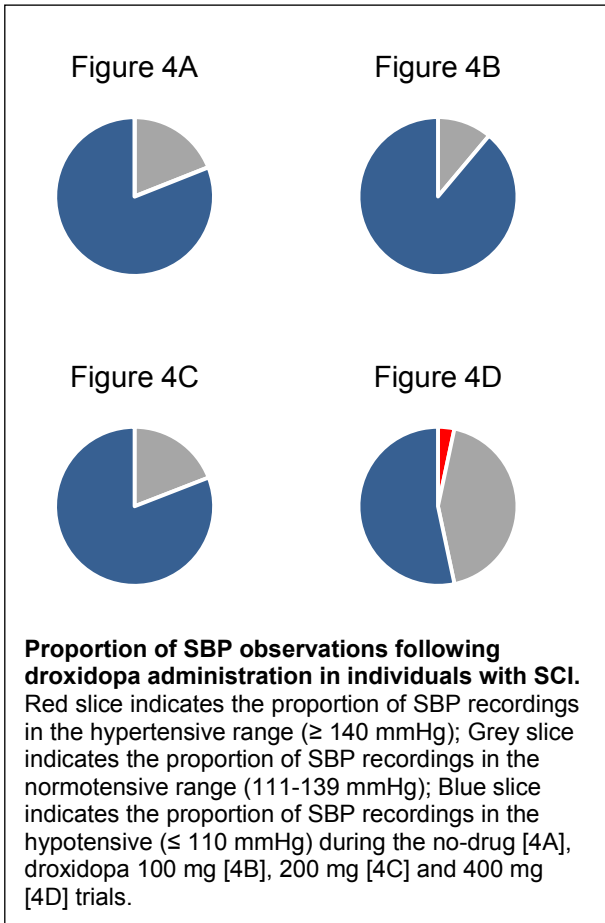
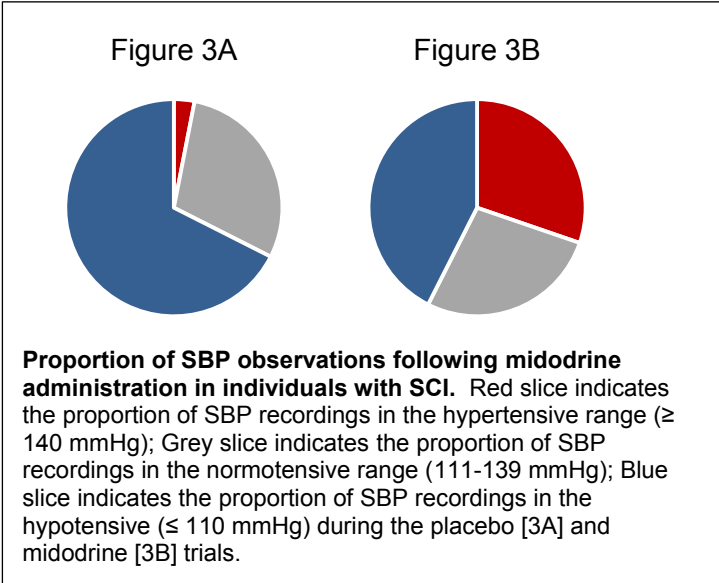
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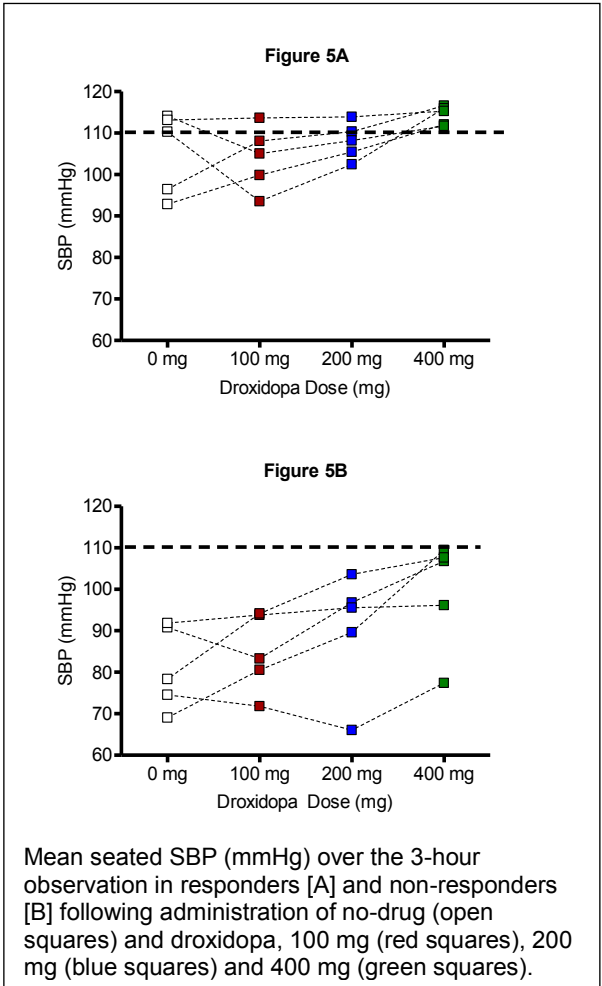
Our group has been interested in increasing the armamentarium of safe and effective pharmacological treatment options for asymptomatic hypotension and OH for use in the SCI population for over a decade [4, 16, 25, 62, 63, 103, 104, 109, 120] and we have advanced the field of study to a greater extent than any other group. Midodrine is the most commonly prescribed anti-hypotensive agent used to treat symptomatic hypotension and OH in the SCI population. In 2013, we were funded by the VA Rehabilitation Research & Development Service and the Craig H. Neilsen Foundation to study the effects of midodrine (10 mg) on seated SBP, CBFv and performance on a memory task in veterans and non-veterans with SCI in a randomized,

double-blind, placebo-controlled trial. Preliminary data on the mean seated SBP response to midodrine compared to placebo is presented in 21 hypotensive subjects with SCI (**Figure 1**). The results suggest significantly elevated SBP following midodrine (10 mg) administration compared to the other 3 conditions; however, individuals responses to midodrine varied significantly (**Figure 2**). In fact only one-third of the subjects tested (7 subjects) responded to midodrine with a normal SBP (between red dashed lines); 7 remained hypotensive and 7 had hypertensive responses. Furthermore, compared to placebo (**Figure 3A**), the percentage of SBP recordings reflecting systolic hypertension (i.e., ≥ 140 mmHg) following midodrine administration (**Figure 3B**) was significantly increased ($p<0.01$) over the 4-hour observation, whereas the percent of normotensive SBP observations was unchanged. Collectively these data suggest that midodrine is effective at normalizing SBP in some hypotensive individuals with SCI, but resulted in seated systolic hypertension in one-third of the population tested.

Droxidopa is a prodrug that is converted to NE, which binds to alpha-receptors and causes increases in orthostatic BP. We have demonstrated that 400 mg oral administration of droxidopa significantly increases seated SBP in hypotensive individuals with SCI; however, individual responses varied. [16] The proportion of SBP recordings within the normotensive range (i.e., 111-139 mmHg) did not differ from the no-drug trial (**Figure 4A**) following administration of either the 100 mg (**Figure 4B**) or 200 mg (**Figure 4C**) dose of droxidopa; however, the 400 mg dose (**Figure 4D**) did appear to increase the proportion of normal SBP recordings ($42.3 \pm 28.5\%$) over a 3-hour seated observation compared to the no-drug ($19.3 \pm 29.5\%$), 100 mg ($11.8 \pm 23.3\%$) and 200 mg ($18.9 \pm 21.8\%$) trials, although this difference was not statistically significant. Three individuals each had a single recording of a seated SBP ≥ 140 mmHg (156, 150, 149 mmHg), which was observed during the first 30-minutes, and constituted 3% of all observed SBP recordings (**Figure 4D**). Individual seated SBP responses (mmHg) to droxidopa, averaged over the 3-hour observation, is presented (**Figure 5**). As depicted (**Figure 5A**), 5 individuals responded to the 400 mg dose with a SBP \geq



110 mmHg (i.e., normotensive) and 5 individuals remained hypotensive (**Figure 5B**). Baseline seated SBP was



significantly increased in those who responded to the 400 mg dose of droxidopa compared to the non-responders (105±10 vs. 81±10 mmHg, respectively; p=0.0048), and although the magnitude of effect was doubled in the non-responders, the SBP response did not differ significantly (9.0±10 vs. 18.6±16 mmHg, respectively; p=0.2937). These data suggest that individuals with a seated SBP below 95 mmHg may need a higher dose of droxidopa to normalize SBP.

d) Research Design and Methods

We propose to determine the dose of droxidopa that normalizes seated SBP in hypotensive individuals with SCI, and to determine the effect of that dose of droxidopa on supine BP, orthostatic BP and CBFv compared to placebo.

Study Population: Fifty subjects with SCI will be screened for study eligibility. We anticipate that approximately 40 of the subjects screened will be eligible and will undergo the dose optimization trial (**Study 1**). We anticipate that 25 subjects will respond to droxidopa with a normal seated SBP, and these individuals will be eligible for the randomized placebo-controlled trial to determine the effect of the optimal dose on supine BP, orthostatic BP and CBFv compared to placebo (**Study 2**). Each subject will be randomized by the Research Pharmacy to receive either droxidopa/placebo or placebo/droxidopa for the placebo-controlled prospective trial. Randomization will occur in a double-blinded manner. Study medication and placebo will be distributed by the James J Peters VAMC Pharmacy Service. The study is proposed to be completed in two years. Total enrollment will be accomplished within 18 months of obtaining full IRB approval, which should be complete within 6 months of funding, and subject participation is estimated to last about 6-8 weeks. A complete description of the study population can be found in the Human Subjects Form 11.

Study Procedures: Identical testing procedures will be performed at the JJP VAMC and the ISMMS according to the table below.

| Procedures Table | Screening | Study 1 | | | | | | | | Study 2 | |
|--------------------|-----------|---------|---|---|---|---|---|---|---|---------|----|
| | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Visit | 1 | | | | | | | | | | |
| Medical Intake | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| OH Survey | X | | | | | | | | | | |
| AD Survey | X | | | | | | | | | | |
| Seated BP | X | X | X | X | X | X | X | X | X | X | X |
| Supine BP | X | | | | | | | | | X | X |
| HUT BP | | | | | | | | | | X | X |
| CBFv | | | | | | | | | | X | X |
| Side-effects | | X | X | X | X | X | X | X | X | X | X |
| OH Symptoms Survey | | | | | | | | | | X | X |
| Fatigue Survey | X | | | | | | | | | X | X |

Screening Visit – Individuals with SCI will be approached by investigators and asked to provide informed consent to participate in a screening study to determine eligibility. Compression garments will be removed, if tolerated, prior to assessment of supine and seated BP.

Any subject taking a vasoconstrictor agent will be asked to stop these medications 2 days or 5 half-lives (whichever is longer) prior to the screening visit, if medically cleared. The screening assessments will include: medical intake information (Appendix 1), medical history (Appendix 2), physical examination, American Spinal Cord Injury Impairment Scale (AIS) classification (if not assessed in the prior 6-months), clinical symptoms survey for OH and AD (Appendix 3) and

brachial BP assessment, recorded one time per minute for 10 minutes while in the seated and supine positions. Individuals will be eligible to participate in the study if 1) the average seated BP meets the WHO definition of hypotension (i.e., SBP \leq 110 mmHg for males or SBP \leq 100 mmHg for females) or 2) there is evidence of OH (i.e., orthostatic fall in BP \geq 20/10 mmHg when moved from the supine to the seated position) and 3) there is no evidence of sustained elevation in BP \geq 140/100 mmHg in either the supine or seated positions. This visit will take about 2 hours.

Study 1– To determine the proportion of subjects with SCI with: 1.1) a normotensive response to droxidopa and 1.2) a sustained hypertensive response to droxidopa. The dose optimization study will be scheduled to begin after completion of the screening visit. Eligible participants will be administered oral droxidopa in a dose escalation, open-label manner beginning with 200 mg. The dose will be adjusted upwards by 100 mg on subsequent visits until (1) average SBP recorded 60-120 minutes after dose administration is 111-139 mmHg in males and 101-139 mmHg in females (i.e., normotensive), (2) sustained elevation (\geq 30 consecutive minutes) in seated SBP \geq 140/100 mmHg, (3) maximum dose of 800 mg is reached without adequate SBP response or (4) intolerable side effects considered related to study medication. Subjects will visit the testing laboratory on as few as 1 (200 mg) and as many as 8 (800 mg) days, and will be asked to refrain from taking prescription anti-hypotensive agents for 12 hours prior to study. Participants with an excessive response to the 200mg dose, i.e., average 4-hour SBP above 139, will be asked to visit the laboratory to determine their blood pressure response to a 100mg dose. Based on our previous data, we do not anticipate an excessive response to the 200mg dose in most participants, we request the addition of the 100mg dose be administered only in participants with excessive responses to the 200mg dose. Subsequent study visits will be scheduled no less than 2 and no more than 10 days apart. Subjects will arrive at the laboratory between 10AM and 1PM after a light breakfast and having avoided alcohol, caffeine, and nicotine for 12-hours. Subjects will remain in their wheelchair for instrumentation, which will include: 1) 3-lead electrocardiogram (ECG) for continuous recording of heart rate (HR) and respiration rate; 2) brachial BP, which will be monitored using a manual sphygmomanometer and finger arteriolar beat-to-beat BP, which will be recorded using photoplethysmography with a cuff placed around the middle or index finger of the left hand. Seated cardiovascular hemodynamic assessments will be monitored and recorded at 15-minute intervals for 4-hours, and the side effects questionnaire (Appendix 4) will be administered hourly during the 4-hour study. Individuals who do not respond to droxidopa with a normal seated SBP will be excluded from Study 2. Each study visit will take about 5 hours.

Following identification of the optimal dose subjects will undergo a washout period of no less than 2 and no more than 10 days. The minimum 2-day washout was chosen because of the known 2- to 3-hour plasma half-life of droxidopa. [17]

Study 2 – To determine the effect of droxidopa, compared to placebo, on: 2.1A) supine SBP (mmHg); 2.1B) proportion of supine BP observations \geq 140/100 mmHg; 2.2) SBP during a HUT and 2.3) change in CBFv from supine to HUT. Within about 1 week of determining the dose of droxidopa that normalizes seated SBP eligible participants will return to the laboratory for the placebo-controlled randomization trial. Subjects will arrive at the laboratory between 10AM and 1PM after a light breakfast and having avoided alcohol, caffeine, and nicotine for 12-hours. Subjects will remain in their wheelchair for instrumentation, which will include: 1) ECG, 2) brachial BP, 3) finger arteriolar BP and 4) CBFv. After instrumentation subjects will be transferred to the supine position (on the tilt table) for a 10-minute period of quiet rest and baseline supine data collection. Participants will then be administered either oral droxidopa or matching placebo in a double-blinded manner and will remain in the supine

position for 60 minutes. Supine HR, finger BP and CBFv will be monitored continuously for 5-minutes at 0, 25 and 55 minutes, supine brachial BP will be monitored and recorded at 0, 10, 20, 30, 40, 50 and 60 minutes. The HUT maneuver will be initiated 60 minutes post-droxidopa/placebo

administration and subjects will remain in the 70° HUT position for 30 minutes or until symptoms of syncope develop. Orthostatic HR, finger BP and CBFv will be monitored continuously for 5-minutes at 0, 10 and 20 minutes during the HUT and brachial BP will be monitored and recorded at 0, 5, 10, 15, 20, 25 and 30 minutes. Additionally, subjects will be asked questions related to the symptoms of OH at 10 minute intervals during the sustained HUT maneuver (Appendix 5). After completion of the HUT maneuver subjects will be transferred to their wheelchair for continued monitoring of seated SBP (until within $\pm 10\%$ of baseline SBP) and will be asked questions pertaining to the side-effects of droxidopa (Appendix 4). Because hypotensive individuals with SCI self-report an increased incidence of fatigue, we will assess fatigue using the Visual Analog Fatigue Scale (VAFS) during the two visits to determine if BP elevation, with droxidopa, reduces fatigue symptoms compared to placebo (Appendix 6). These visits will take about 5 hours.

Cardiovascular Assessments:

- **Electrocardiogram** - A 3-lead ECG (UFI: model RESP 1, Morro Bay CA) will be used to measure beat-to-beat HR and respiration rate (RR) during testing. Electrodes will be placed at the right and left clavicle and in the V-5 position; data will be recorded from V-5. HR and RR signals will be viewed in real time and will be stored for analysis of cardiovascular autonomic control (via heart rate variability techniques: HRV) using customized programs written with LabView graphical software.
- **Finger Arteriolar Blood Pressure** Beat-to-beat BP will be continuously monitored from the left middle or ring finger using photoplethysmography (FMS: Finometer, Pro; Amsterdam, Netherlands). Finger arteriolar BP will be viewed in real time on a computer screen during the supine, seated and HUT observation periods and will be stored for analysis to estimate sympathetic influences on vascular control (BP variability: BPV) using customized programs written with LabView graphical software.
- **Brachial Blood Pressure** - Brachial BP will be measured by a trained technician using a standard adult BP cuff (GE Healthcare Information Technologies, Milwaukee, WI) with a manual sphygmomanometer at 5-15 minute intervals during studies 1 and 2.

Cerebrovascular Assessments:

- **Cerebral Blood Flow Velocity** – will be monitored using Transcranial Doppler (TCD) ultrasound (Terumo Cardiovascular Systems 1311 Valencia Avenue Tustin, CA 92780-6447) to assess blood flow velocity (cm/s) at the left middle cerebral artery (MCA) through the temporal window. The MCA signature will be identified by the depth (45-55 mm), sound and direction of flow (towards the probe), as evidenced by the color and spectral waveform. The TCD probe will be operated at a frequency of 2.0 MHz to visualize the MCA through the temporal window; once visualized, a head-harness will be used to secure probe placement for the duration of testing. TCD recordings of CBFv will be viewed in real-time continuously throughout testing and will be recorded at intervals described above. The raw analog CBFv signal will be digitized and stored for subsequent analysis using customized programs created with LabView graphical software.

Blood Draws:

- Four plasma samples (20 mL per sample) will be drawn from an antecubital vein for analysis of changes in plasma renin, serum aldosterone and plasma norepinephrine concentrations following administration of droxidopa compared to placebo. Concentration of these vasoactive substances are altered during orthostatic provocation, which may be differentially affected by study drug compared to placebo.

Surveys

- **Vancouver Coastal Health Autonomic Dysfunction following SCI Survey** (Appendix 3) - will be used to determine the frequency and severity of the common symptoms and side effects of AD and OH.
- **Side-Effects Survey** (Appendix 4) – The most common side-effects reported with droxidopa are headache (%) dizziness (%) nausea (%) hypertension (%) and fatigue. In addition, subjects may report: feeling feverish, muscle cramps, confusion and uncontrolled movements. Therefore, we will ask participants questions related to these known side-effects and will gather data on any other subject symptom that may be related to the study medication.
- **The Visual Analog Fatigue Scale** (Appendix 5) – will be used one time per study visit to determine the effects of droxidopa dose (Study 1) compared to placebo (Study 2) on self-report severity of fatigue.

Data Analysis:

This is a pilot trial to determine the dose efficacy and safety of droxidopa to increase systemic BP and improve orthostatic BP and CBFv responses compared to placebo in hypotensive individuals with SCI. Because this is a pilot trial, the following statistical analyses are not powered for a specific effect size; however, the results will be used to power a subsequent large scale clinical trial to identify the utility and safety of droxidopa for treatment of asymptomatic hypotension in persons with SCI.

Primary Aim 1.1: Dose optimization, open-label trial to determine the proportion of subjects with SCI with a normotensive response to droxidopa (**Efficacy #1**). Normotension will be defined as an average systolic BP (SBP) recorded 60-120 minutes after dose administration of between 111-139 mmHg in males and 101-139 mmHg in females.

- **Hypothesis 1.1** – Seated SBP will be normalized in 60% of the study sample following administration of droxidopa.
 - This hypothesis will be tested by constructing a 95% confidence interval about the sample proportion of cases in which BP is normalized with droxidopa. The inclusion of the 60% value in the confidence interval will be taken as evidence in support of the hypothesis. Further, the point estimate and confidence interval will provide the first reported estimate of the BP normalizing effect of droxidopa in the population with SCI.

Primary Aim 1.2: Dose optimization, open-label trial to determine the proportion of subjects with SCI with a hypertensive response to droxidopa (**Safety #1**). Hypertension will be defined as a sustained elevation in seated SBP $\geq 140/100$ mmHg or intolerable side effects considered related to study medication

- **Hypothesis 1.2** – Less than 10% of the study sample will exhibit hypertension or intolerable side effects related to administration of droxidopa.

- This hypothesis will be tested by constructing a 95% confidence interval about the proportion of cases in which either seated BP \geq 140/100 or intolerable side effects occur. If the 95% CI excludes values \geq 10%, this will be taken as evidence in support of the hypothesis. Further, the point estimate and confidence interval will provide the first reported estimate of the expected side effects of droxidopa treatment in the population with SCI.

Secondary Aims: To determine the effect of the individualized optimal dose of droxidopa, compared to placebo, on (1) supine BP (**Safety #2**), (2) SBP during a head-up tilt (HUT) maneuver to 70° (**Efficacy #2**) and change in cerebral blood flow velocity (CBFv) from supine to HUT (**Efficacy #3**). The following hypotheses will be tested in hypotensive individuals with SCI:

- **Hypothesis 2.1A** – Average supine SBP will be significantly increased following droxidopa administration compared to placebo.
 - This hypothesis will be tested using a repeated measures analysis of covariance where the pre-droxidopa or placebo SBP will be used as the covariate and the adjusted post-test scores will serve as the dependent variable. In addition, the covariate adjusted point estimate and 95% confidence interval of the difference between drug conditions will provide the first reported estimate of the supine SBP response to droxidopa versus placebo in the SCI population.
- **Hypothesis 2.1B** – The proportion of supine BP observations \geq 140/100 mmHg following droxidopa administration will not differ significantly from the proportion observed during the placebo trial.
 - This hypothesis will be tested by performing separate (one each for systolic and diastolic pressure) tests of the differences between dependent proportions, from which the 95% confidence intervals will be calculated. The presence of zero in a confidence interval will indicate a lack of statistical difference in incidence of hypertensive events between the droxidopa and placebo conditions.
- **Hypothesis 2.2** – Average SBP during 70° HUT will be significantly increased following droxidopa administration compared to placebo.
 - This hypothesis will be tested by performing a dependent t-test between the mean SBP during 70° HUT comparing droxidopa to placebo. Further, the point estimate and resulting 95% confidence interval will provide an estimate of the SBP response to HUT of droxidopa versus placebo in the SCI population.
- **Hypothesis 2.3** – The change in CBFv from supine to HUT will be significantly attenuated following droxidopa administration compared to placebo.
 - This hypothesis will be tested using a repeated measures analysis of covariance where the pre-HUT CBFv will be used as the covariate and the adjusted post-HUT CBFv scores will serve as the dependent variable. In addition, the covariate adjusted point estimate and 95% confidence interval of the differences between drug conditions (droxidopa vs. placebo) will provide the first reported estimate describing the effect of droxidopa on the CBFv response to HUT.
- **Hypothesis 2.4** – Plasma renin and serum aldosterone concentrations will be reduced and plasma norepinephrine concentrations will be increased during HUT following administration of droxidopa compared to placebo.
 - These hypotheses will be tested using a repeated measures analysis of covariance where the pre-HUT concentrations will be used as the covariate and the adjusted post-HUT concentrations will serve as the dependent variable. In addition, the covariate adjusted point estimate and 95% confidence interval of the differences between drug conditions (droxidopa vs. placebo) will provide the first

reported estimate describing the effect of droxidopa on these vasoactive substances in response to HUT.

Safety Monitoring:

As is stated in the consent forms there is a risk of increased systemic blood pressure following administration of droxidopa.

Laboratory Monitoring: During the laboratory observation heart rate and blood pressure will be closely monitored at 15 minute intervals and action will be taken if blood pressure is elevated above 140/90 mmHg for more than 30 minutes. The action plan to lower blood pressure in the laboratory is as follows:

1. Loosening of clothing or braces
2. Re-positioning the participant in his/her wheelchair
3. Emptying of the bladder/catheter bag

If these measures prove unsuccessful in lowering blood pressure the study physician will be alerted and brought to the laboratory for further subject monitoring and administration of an anti-hypertensive agent if deemed necessary. The medication of choice will be sub-lingual nitroglycerin.

The study clinician, William Bauman, MD will monitor and review all blood pressure recordings during each laboratory visit in both Study 1 and 2. Although he will not be in the laboratory for the duration of testing, his office is across the hall and he is readily accessible if needed. Testing will be scheduled when Dr. Bauman is in the office only.

Because Study 2 is a randomized blinded placebo controlled trial we have included a data safety monitor to review individual blood pressure responses and trends in hemodynamic and symptoms in aggregate data. Dr. Noam Y. Harel, MD will be an independent clinical monitor, he will have a copy of the randomization code and will contact study investigators if a concern arises pertaining to a study participant and will be in contact with the participant who may be experiencing increased symptoms related to AD.

Home Monitoring: Participants will be monitored for 4 hours or until their blood pressure has returned to baseline levels ($\pm 10/5$ mmHg). No subject will be sent home with a blood pressure that is elevated above 140/90 mmHg. However, if blood pressure remains above their baseline, **but not in the hypertensive range**, after 4-hours of testing they may be sent home with a 24-hour blood pressure monitor, which will be programmed to obtain a blood pressure reading every 20 minutes during the day and at 30-minute intervals during the night. The study coordinator or the PI will follow-up by phone with the subject to assess any adverse side effects and to document blood pressure changes. The subject will be asked to immediately report any significant AE they may feel after leaving the laboratory.

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