Effectiveness of droxidopa compared to midodrine in standing blood pressure and orthostatic tolerance in adults with neurogenic orthostatic hypotension: a systematic review protocol

Kelli Patrick1,2 - Tina Martin1,2

1 School of Nursing, University of Mississippi Medical Center, Jackson, USA, 2 UMMC School of Nursing Evidence Based Practice and Research Team: a Joanna Briggs Institute Affiliated Group

Review question: The question of this review is: what is the effectiveness of droxidopa compared to midodrine on standing blood pressure and orthostatic intolerance symptoms in adults with neurogenic orthostatic hypotension?

Keywords droxidopa; midodrine; neurogenic orthostatic hypotension; orthostatic intolerance; standing blood pressure


Background

Upon standing, a complex mechanism of responses by the autonomic nervous system, works to ensure that adequate blood volume continues to circulate the human body, preventing almost a liter of blood from pooling in the extremities and abdomen.1-3 Normally, blood pressure is maintained at a similar level, whether the individual is supine, sitting or standing.1,3 However, when this normal response to standing fails, a drop in standing blood pressure occurs, known as orthostatic hypotension.1,3 Orthostatic hypotension (OH) is defined as a continuous decrease of blood pressure (BP) of at least 20 mmHg systolic or 10 mmHg diastolic within three minutes of standing or a head-up tilt of at least 60 degrees.2-4-8 The mechanism behind this drop in blood pressure can have several causes.2-7 Both non-neurogenic and neurogenic causes of OH can occur and can be chronic or acute.1,2,7-9 Neurogenic orthostatic hypotension (NOH) is characterized by impaired vasoconstriction due to inadequate release of norepinephrine from sympathetic vasomotor neurons.1,7,10-12 Neurogenic orthostatic hypotension occurs primarily in autonomic degenerative disorders such as Parkinson’s disease (PD), Lewy body dementia, multiple system atrophy (MSA) and pure autonomic failure (PAF), which are characterized by abnormal accumulations of alpha-synuclein.1,2,7,8,10,13,14 Peripheral neuropathies such as diabetic neuropathy, amyloidosis, and Guillain Barre syndrome can also cause NOH.1,14 In fact, the most common cause of secondary autonomic dysfunction, which is a mechanism behind NOH, is diabetes mellitus.15 Non-neurogenic orthostatic hypotension can be caused by non-neurological based mechanisms such as medication side effects, blood loss, deconditioning or dehydration.1,2,5

Approximately 80,000 patients with PD, MSA or PAF are affected by NOH.1 Half of patients with Lewy body dementia and 75% of patients with MSA will have NOH.1,2,10 According to the Rochester Diabetic Neuropathy Study, 8.4% of type I diabetics and 7.4% of type II diabetics had OH in the population studied.1 Orthostatic hypotension associated hospitalization rates in 2004 were 36 per 100,000 adults in the United States.1 Patients with OH have significantly higher rates of morbidity and mortality, and NOH patients have a higher risk for cardiovascular events.5,9,10 Although higher mortality rates can be seen in patients with NOH, a major component of NOH is patients experiencing a decreased quality of life (QOL).1,2,9 Compared to patients with OH due to other causes, patients with NOH tend to
have more severe symptoms such as dramatic drops in blood pressure during the day and postprandial hypotension.\textsuperscript{1} Activities as simple as eating, exposure to warm ambient temperatures and exercise can exacerbate symptoms in patients with NOH.\textsuperscript{1,2,8,13} There is documentation of patients with severe NOH due to autonomic failure having a high incidence of fractures and trauma caused by falls.\textsuperscript{16} Symptoms of NOH can be debilitating and negatively impact a patient’s quality of life.\textsuperscript{2,17,18} Patients with OH can have feelings of isolation and loss of independence, often associated with the increase risk factor for falls and syncope that accompanies OH.\textsuperscript{17} Orthostatic dizziness and syncope, classic NOH symptoms, along with lesser understood symptoms such as coat-hanger pain in the neck and shoulders, and cognitive impairment can force patients to limit activities which involve standing or walking.\textsuperscript{1,2,13,14,16} Therefore, the goals of NOH treatment are to reduce symptoms, improve functional ability and QOL, and reduce the occurrence of falls and syncope.\textsuperscript{13,16}

Initial diagnosis of NOH is based on blood pressure and heart rate measurements taken after the patient is supine for at least five minutes, and then after one and three minutes of standing.\textsuperscript{1,2} Clinical diagnosis is confirmed through autonomic testing.\textsuperscript{1} “During continuous blood pressure monitoring of the Valsalva maneuver, a diagnosis of NOH is indicated by an exaggerated and sustained decreased in blood pressure without a compensatory increase in heart rate during straining (phase 2), a lack of reflex vasoconstriction shown through a loss of late phase 2 and blood pressure overshoot, and delayed blood pressure recovery.”\textsuperscript{1}(p.5252-3) Symptoms experienced by patients can be documented using self-report questionnaires. Symptoms addressed by the questionnaires used in studies of midodrine and droxidopa include the presence of syncope/pre-syncope, dizziness/light headedness, weakness/fatigue, and ability to remain upright.\textsuperscript{10,14,18} A global assessment of symptom relief is also used in many studies. Three tools used in recent studies to assess these symptoms include the Orthostatic Hypotension Symptom Assessment (OSHA), the Orthostatic Grading Scale (OGS) and the Orthostatic Hypotension Questionnaire (OHQ) which have been used in clinical trials to measure efficacy of interventions for NOH.\textsuperscript{1,10,14,18,19}

Treatments for NOH include non-pharmacologic and pharmacologic measures.\textsuperscript{2,3,9} Non-pharmacologic measures used to treat NOH include the use of compression stockings, abdominal binders and counter maneuvers to decrease blood pooling.\textsuperscript{1,2,8,16,20} Ensuring adequate fluid intake of at least two liters per day along with increasing salt intake to up to ten grams per day can attenuate some symptoms by increasing blood volume.\textsuperscript{1,2,8,20} Only two sympathomimetic medications have been approved by the United States (US) Food and Drug Administration (FDA) for treatment of NOH: droxidopa and midodrine.\textsuperscript{4,12,16} These medications are used to reduce orthostatic symptoms, improve QOL and prevent falls.\textsuperscript{2,14,16}

“Droxidopa is a synthetic amino acid precursor that is converted by aromatic l-amino acid decarboxylase into norepinephrine.”\textsuperscript{14}(p.198) It acts to increase the levels of norepinephrine in postganglionic sympathetic neurons, leading to increased stimulation of adrenergic receptors.\textsuperscript{10,11,14,15} The most common adverse event seen in the use of droxidopa is supine hypertension.\textsuperscript{15} Droxidopa was first developed for use by Sumitomo Pharmaceuticals in Japan and has been approved in Japan since 1989 for the treatment of neurogenic orthostatic hypotension.\textsuperscript{4,5,14,13,19} Droxidopa was approved for use in the US by the FDA in 2014 for the treatment of symptomatic NOH caused by primary autonomic failure, dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.\textsuperscript{10,14,16,19}

Midodrine works by selectively and directly stimulating alpha 1-adrenergic receptors located on the arteriolar and venous vasculature.\textsuperscript{15,18} Midodrine is a prodrug that is metabolized to an active metabolite, desglymidodrine, which acts peripherally and does not cross the blood brain barrier.\textsuperscript{16,20} The most common side effects/adverse events reported with midodrine use include supine hypertension, pruritus/tingling, urinary urgency and headache.\textsuperscript{18} Midodrine was approved in the US in 1996 and in the United Kingdom in 2015 for treatment of orthostatic hypotension.\textsuperscript{3,4,6} Until the approval of droxidopa in 2014, midodrine was the only FDA approved medication for the treatment of NOH in the US.\textsuperscript{1} Midodrine is still the only approved sympathomimetic medication used in the treatment of NOH in the United Kingdom.\textsuperscript{6}

Both midodrine and droxidopa have been shown to decrease symptoms of orthostatic tolerance and increase standing BP.\textsuperscript{1,2,5,6,10,12,13} However, the two medications have not been directly compared.
Experimental studies comparing the effects of these two medications will give healthcare providers best practice data for treatment outcomes. Though these two medications have different mechanisms of action, they have the same treatment goals. Systematic reviews on each individual medication have been published; however, these two medications have not been compared to each other. A preliminary search was conducted in the JBI Database of Systematic Reviews and Implementation Reports, Cochrane, PubMed, PROSPERO and DARE in September 2016 and no other current or underway systematic reviews on the topic were found. The debilitating symptoms present in patients with NOH makes this systematic review imperative in order to guide future best practice.

Inclusion criteria

Participants
This review will consider studies that include adults aged 18 and over with a diagnosis of neurogenic orthostatic hypotension. This study will exclude patients with non-neurogenic orthostatic hypotension.

Intervention(s)
This review will consider studies that evaluate the use of droxidopa to treat neurogenic orthostatic hypotension. Any dose and frequency of the medication will be included.

Comparator(s)
This review will compare the intervention to studies which evaluate the use of midodrine as a treatment for neurogenic orthostatic hypotension. Any dose and frequency of the medication will be included.

Outcomes
This review will consider studies that include the following outcomes: standing blood pressure and orthostatic intolerance symptoms. Changes in blood pressure measurements from supine to standing position will be the primary outcome evaluated. Secondary outcomes to be evaluated include orthostatic intolerance symptoms and reported side effects/adverse events of each medication. Side effects/adverse events to be addressed include but are not limited to headache, pruritus/tingling and supine hypertension. Patient self-reporting of global orthostatic symptoms along with specific symptom evaluation such as syncope/pre-syncope, dizziness/light headedness, weakness/fatigue, and ability to remain upright will be used as secondary outcomes. These outcomes are measured using a global symptom relief score, the Orthostatic Hypotension Symptom Assessment (OSHA), the Orthostatic Grading Scale (OGS) and the Orthostatic Hypotension Questionnaire (OHQ), or a self-reported symptom assessment.

Study types
This review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. Studies published in English will be included. Studies published since 1970 will be included as studies on midodrine and droxidopa began during this period with further research continuing until today.

Search strategy
The search strategy will aim to find both published and unpublished studies. An initial limited search of PubMed and CINAHL has been undertaken to identify articles on this topic, followed by analysis of the text words contained in the titles and abstracts, and of the index terms used to describe these articles. This informed the development of a search strategy including identified keywords and index terms which will be tailored for each information source. A full search strategy for each database is detailed in Appendix I. The reference list of all studies selected for critical appraisal will be screened for additional studies.

Information sources
The databases to be searched include: PubMed, Embase, CINAHL and Scopus
The trial registers to be searched include: Cochrane Library CCTR and ClinicalTrials.gov
The search for unpublished studies will include: Google, MedNar, WorldWideScience, ProQuest Theses and Dissertations.

Study selection
Following the search, all identified citations will be collated and uploaded into EndNote and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that may
meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute’s System for the Unified Management, Assessment and Review of Information (JBI SUMARI). The full text of selected citations will be retrieved and assessed in detail against the inclusion criteria by two independent reviewers. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Critical appraisal
Selected studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for experimental and quasi-experimental studies. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

Data extraction
Data will be extracted from papers included in the review using the standardized data extraction tool available in JBI SUMARI by two independent reviewers. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data synthesis
Papers will, where possible be pooled in statistical meta-analysis using JBI-SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) and weighted (or standardized) mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-squared and I² tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufanaru et al. Subgroup analyses will be conducted where there is sufficient data to investigate subgroups such as patient primary diagnoses or patient age. Sensitivity analyses will be conducted to test decisions made regarding the use of droxidopa and midodrine on standing blood pressure and orthostatic tolerance in adults. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

A funnel plot will be generated within JBI SUMARI to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Assessing confidence
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing confidence in the quality of evidence will be used for this review, with the results presented in a summary of findings table created using GRADEPro.

Acknowledgements
This review will contribute toward a Doctor of Nursing Practice (DNP) degree.

References


Appendix I: Search strategy

PubMed


Embase
‘orthostatic hypotension’/exp OR ‘hypostatic hypotension’ OR ‘hypotension, orthostatic’ OR ‘hypotension, postural’ OR ‘iodopathic orthostatic hypotension’ OR ‘orthostatic hypotension’ OR ‘orthostatic insufficiency’ OR ‘orthostatic shock’ OR ‘orthostatic symptom complex’ OR ‘orthostatic syndrome’ OR ‘postural hypotension’ AND (‘droxidopa’/exp OR ‘dops’ OR ‘dextro, levo threo 3, 4 dihydroxyphenylserine’ OR ‘dl threo 3, 4 dihydroxyphenylserine’ OR ‘droxidopa’ OR ‘l threo 3, 4 dihydroxyphenylserine’ OR ‘levo threo 3, 4 dihydroxyphenylserine’ OR ‘northera’ OR ‘threo 3, 4 dihydroxyphenylserine’ serine OR ‘theo 2 amino 3 hydroxy 3 (3, 4 dihydroxyphenyl) propionic acid’ OR ‘theo 3 (3, 4 dihydroxyphenyl) serine’ OR ‘theo 3, 4 dihydroxyphenylserine’ OR ‘threo 3, 4 dihydroxyphenylserine’ OR ‘threo dops’ OR ‘threodops’ OR ‘midodrine’/exp OR ‘1 (2’,5’ dimethoxyphenyl) 2 glycinamidoethan 1 ol hydrochloride’ OR ‘1 (2’,5’ dimethoxyphenyl) 2 glycinamidoethanol hydrochloride’ OR ‘1 (2, 5 dimethoxyphenyl) 2 glycinamidoethanol’ OR ‘2 glycinamidoethanol’ OR ‘2 glycinamidoethan 1 ol hydrochloride’ OR ‘2 glycinamidoethanol’ OR ‘2 glycinamidoethanol’ OR ‘2 glycinamidoethanol’ OR ‘2 glycinamidoethanol’ OR ‘a 4020 linz’ OR ‘a4020 linz’ OR ‘alpha (2, 5 dimethoxyphenyl) beta glycinamidoethanol’ OR ‘alpha glycinamidomethyl 2, 5 dimethoxybenzyl alcohol’ OR ‘almphamine’ OR ‘amatine’ OR ‘dl 1 (2’,5’ dimethoxyphenyl) 2 glucaminidoethan 1 ol hydrochloride’ OR ‘dl 1 (2’,5’ dimethoxyphenyl) 2 glucaminidoethan 1 ol hydrochloride’ OR ‘dl 1 (2’,5’ dimethoxyphenyl) 2 glucaminidoethan 1 ol hydrochloride’ OR ‘dl 1 (2’,5’ dimethoxyphenyl) 2 glucaminidoethan 1 ol hydrochloride’ OR ‘gturon’ OR ‘metligine’ OR ‘midodrine’ OR ‘midodrine’ OR ‘midodrine hydrochloride’ OR ‘midon’ OR ‘midron’ OR ‘midodrine’ OR ‘orvaten’ OR ‘proamatine’ OR ‘st 1085’ OR ‘st1085’)) AND (‘blood pressure’/exp OR ‘blood pressure’ OR ‘blood tension’ OR ‘intravascular pressure’ OR ‘normotension’ OR ‘pressure, blood’ OR ‘vascular pressure’)

CINAHL
Search 1
Search 2

Scopus
((ALL (orthostatic hypotension) AND ALL (droxidopa) AND ALL (blood pressure) AND ALL (orthostatic symptoms))) OR ((ALL (orthostatic hypotension) AND ALL (midodrine) AND ALL (blood pressure) AND ALL (orthostatic symptoms))))
Cochrane Library CCTR
(midodrine OR “midodrine hydrochloride” OR proamatine OR monohydrochloride OR gutron) OR
(droxidopa OR DL-threo-3,4-Dihydroxyphenylserine OR threo-DOPS OR 3,4-threo-DOPS OR 3,4 Dihy-
droxyphenylserine) AND (“orthostatic hypotension” OR “orthostatic intolerance” OR “neurogenic ortho-
static hypotension” OR “postural hypotension”) AND (“blood pressure”)

ClinicalTrials.gov
Search 1
(midodrine OR “midodrine hydrochloride” OR proamatine OR monohydrochloride OR gutron) AND
(orthostatic hypotension OR orthostatic intolerance OR postural hypotension OR neurogenic orthostatic hypotension)
Search 2
(orthostatic hypotension OR orthostatic intolerance OR postural hypotension OR neurogenic orthostatic hypotension) AND (droxidopa OR DL-threo-3,4-Dihydroxyphenylserine OR threo-DOPS OR 3,4-threo-DOPS OR 3,4 Dihydroxyphenylserine)

Google
Search 1
(midodrine OR “midodrine hydrochloride” OR proamatine OR monohydrochloride OR gutron) AND
(“orthostatic hypotension” OR “orthostatic intolerance” OR “neurogenic orthostatic hypotension” OR
“postural hypotension”) AND (“blood pressure”)
Search 2
(droxidopa OR DL-threo-3,4-Dihydroxyphenylserine OR threo-DOPS OR 3,4-threo-DOPS OR 3,4 Dihydroxyphenylserine) AND (“orthostatic hypotension” OR “orthostatic intolerance” OR “neurogenic orthostatic hypotension” OR “postural hypotension”) AND (“blood pressure”)

MedNar
(midodrine OR “midodrine hydrochloride” OR proamatine OR monohydrochloride OR gutron) OR
(droxidopa OR DL-threo-3,4-Dihydroxyphenylserine OR threo-DOPS OR 3,4-threo-DOPS OR 3,4 Dihy-
droxyphenylserine) AND (“orthostatic hypotension” OR “orthostatic intolerance” OR “neurogenic ortho-
static hypotension” OR “postural hypotension”) AND (“blood pressure”)

WorldWideScience
Search 1
(midodrine OR “midodrine hydrochloride” OR proamatine OR monohydrochloride OR gutron) AND
(“orthostatic hypotension” OR “orthostatic intolerance” OR “neurogenic orthostatic hypotension” OR
“postural hypotension”) AND (“blood pressure”)
Search 2
(droxidopa OR DL-threo-3,4-Dihydroxyphenylserine OR threo-DOPS OR 3,4-threo-DOPS OR 3,4 Dihydroxyphenylserine) AND (“orthostatic hypotension” OR “orthostatic intolerance” OR “neurogenic orthostatic hypotension” OR “postural hypotension”) AND (“blood pressure”)

ProQuest Dissertations and Theses
Search 1
(midodrine OR “midodrine hydrochloride” OR proamatine OR monohydrochloride OR gutron) AND
(orthostatic hypotension OR orthostatic intolerance OR postural hypotension OR neurogenic orthostatic hypotension)
Search 2
(orthostatic hypotension OR orthostatic intolerance OR postural hypotension OR neurogenic orthostatic hypotension) AND (droxidopa OR DL-threo-3,4-Dihydroxyphenylserine OR threo-DOPS OR 3,4-threo-
DOPS OR 3,4 Dihydroxyphenylserine)