REVIEW ARTICLE (META-ANALYSIS)

A Systematic Review of the Management of Orthostatic Hypotension After Spinal Cord Injury

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ABSTRACT. Krassioukov A, Eng JJ, Warburton DE, Teasell R, Spinal Cord Injury Rehabilitation Evidence Research Team. A systematic review of the management of orthostatic hypotension after spinal cord injury. Arch Phys Med Rehabil 2009;90:876-85.

Objective: To review systematically the evidence for the management of orthostatic hypotension (OH) in patients with spinal cord injuries (SCIs).

Data Sources: A key word literature search was conducted of original and review articles as well as practice guidelines using Medline, CINAHL, EMBASE, and PsycInfo, and manual searches of retrieved articles from 1950 to July 2008, to identify literature evaluating the effectiveness of currently used treatments for OH.

Study Selection: Included randomized controlled trials (RCTs), prospective cohort studies, case-control studies, pre-post studies, and case reports that assessed pharmacologic and nonpharmacologic intervention for the management of OH in patients with SCI.

Data Extraction: Two independent reviewers evaluated the quality of each study, using the Physiotherapy Evidence Database score for RCTs and the Downs and Black scale for all other studies. Study results were tabulated and levels of evidence assigned.

Data Synthesis: A total of 8 pharmacologic and 21 nonpharmacologic studies were identified that met the criteria. Of these 26 studies (some include both pharmacologic and nonpharmacologic interventions), only 1 pharmacologic RCT was identified (low-quality RCT producing level 2 evidence), in which midodrine was found to be effective in the management of OH after SCI. Functional electrical stimulation was one of the only nonpharmacologic interventions with some evidence (level 2) to support its utility.

Conclusions: Although a wide array of physical and pharmacologic measures are recommended for the management of OH in the general population, very few have been evaluated for use in SCI. Further research needs to quantify the efficacy of treatment for OH in subjects with SCI, especially of the many other pharmacologic interventions that have been shown to be effective in non-SCI conditions.

Key Words: Hypotension; orthostatic; Rehabilitation; Review [publication type]; Spinal cord injuries.

THE DEFINITION OF *orthostatic hypotension* is typically accepted as a decrease in systolic blood pressure of 20mmHg or more, or a reduction in diastolic blood pressure of 10mmHg or more, on changing body position from a supine position to an upright posture, regardless of the presence of symptoms.[1] Numerous studies have documented the presence of OH after SCI.[2-5] OH is more common in tetraplegia than paraplegia, with prevalence rates as high as 82% for tetraplegia versus 50% for those with paraplegia immediately post-SCI.[5] This condition not only is evident in the acute period postinjury but also has persisted in a significant number of persons for many years.[6-8] Standard mobilization during physiotherapy (eg, sitting or standing) is reported to induce blood pressure decreases that are diagnostic of OH in 74% of patients with SCI, and which are accompanied by OH symptoms (like lightheadedness or dizziness) (appendix 1) in 59% of patients with SCI.[5] This in turn may have a negative impact on the ability of subjects with SCI to participate in rehabilitation. Current management approaches for the treatment of OH consist of pharmacologic and nonpharmacologic interventions.

The low level of efferent sympathetic nervous activity and the loss of reflex vasoconstriction after SCI are among the major causes of OH. The decrease in arterial blood pressure after a change to an upright position in subjects with SCI appears to be related to excessive pooling of blood in the abdominal viscera and lower extremities.[2,6,9] The excessive venous pooling in the lower extremities, and the reduced blood volume in the intrathoracic veins, ultimately lead to a decrease in end-diastolic volume, and thus a decrease in left ventricular stroke volume.[10] A subsequent reduction in cardiac output and arterial pressure may lead to tachycardia. However, this reflex tachycardia is often insufficient to compensate for the lowered output and pressure. Consequently, the pooling of blood in the lower extremities and the decrease in blood pressure may result

List of Abbreviations

FES	functional electrical stimulation
L-DOPS	L-threo-3,4-dihydroxyphenylserine
NO	nitric oxide
OH	orthostatic hypotension
PEDro	Physiotherapy Evidence Database
RCT	randomized controlled trial
SCI	spinal cord injury

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in a reduction in cerebral flow, which presents as the signs and symptoms of OH (see appendix 1).

In addition to central causes of OH after SCI, there also is some evidence suggesting that changes in the periphery, such as upregulation of the potent vasodilator, NO, might contribute to orthostatic intolerance in this population.[11] In experimental animals, it has been demonstrated that NO synthase expression is dysregulated after SCI.[12] Furthermore, Wecht et al[13] found that intravenous infusion of NO synthase inhibitors facilitates the normalization of blood pressure in subjects with SCI.

Several other factors may predispose persons with SCI to OH, including low plasma volume, hyponatremia, and cardiovascular deconditioning caused by prolonged bed-rest (appendix 2).[2,5,6] In addition, the prevalence of OH is more common in tetraplegia,[2,7,8] and in persons who have sustained a traumatic SCI versus those whose cord damage has been nontraumatic, as with cervical spinal stenosis.[14]

Most of our understanding of the pathophysiology and management of OH is derived from the management of this condition in subjects with central autonomic neurodegenerative disorders (eg, multiple system atrophy, Parkinson disease) and patients with peripheral autonomic disorders (eg, autonomic peripheral neuropathies, pure autonomic failure).[2,15] From previous studies in subjects without SCI, it is well established that a combination of patient education and the use of pharmacologic and nonpharmacologic modalities can lead to the successful management of OH. The therapeutic goal for management of OH is not to normalize the blood pressure values; rather, it is to ameliorate symptoms while avoiding side effects.[16] The deleterious effects of low blood pressure such as a greater risk of developing pressure ulcers as a result of reduced tissue perfusion,[17] and an increased dependence on the renin-angiotensin system, as a result of renal hypoperfusion, provide reasons to consider normalizing blood pressure independent of OH symptoms. The current general approach in the management of OH is to implement therapeutic interventions in stages, dependent on the severity of symptoms.[16] It is well known from previous studies in non-SCI populations that nonpharmacologic measures alone often are insufficient to render OH asymptomatic. However, given that the mechanisms of OH development appear to be different in patients with SCI, it is important to assess the effectiveness of treatment strategies specific to patients with SCI. The following systematic review was conducted to provide health care professionals with the evidence that supports the efficacy of the various strategies currently used to prevent and manage OH in the SCI population. In addition, identifying gaps in the evidence can help direct research efforts to areas of priority. These findings were part of the Spinal Cord Injury Rehabilitation Evidence project (the details of which are available at *http://www.icord.org/scire/*).

METHODS

A key word literature search of original articles, previous practice guidelines, and review articles was conducted to identify literature published from 1950 to July 2008 evaluating the effectiveness of any treatment or therapy for OH in the SCI population. The population key words *spinal cord injury*, *paraplegia*, and *tetraplegia* were individually paired with *orthostatic hypotension*, *orthostatic intolerance*, and *blood pressure*. Studies that did not have outcomes evaluating OH—like blood pressure or OH symptoms (eg, light-headedness, dizziness)—were excluded.

The quality of each study was scored by 2 independent reviewers. The 11-item PEDro[18] was used to score RCTs. Note that question 1 (external validity, whether eligibility criteria were specified) is not part of the final score. The PEDro score comprises questions 2 through 11, which address internal validity (eg, blinding of assessors), with higher scores (maximum 10) indicating better methodologic quality (9–10=excellent; 6–8=good; 4–5=fair; <4=poor).[19] A modified version of the Downs and Black evaluation tool[20] was used to score trials that were not randomized. Again, higher scores indicate a better quality study; for the modified version, the highest score that could be assigned to any study was 28.[20]

The description by Sackett et al[21] of levels of evidence was used to draw conclusions about the level of evidence for the accumulated studies. Sackett's[21] levels of evidence were collapsed into 5 categories, whereby evidence was rated level 1 if derived from good to excellent RCTs with PEDro scores of 6 or higher, level 2 if derived from RCTs with PEDro scores of 5 or less or from nonrandomized prospective controlled and cohort studies, level 3 if derived from case-control studies, level 4 if derived from either pre-test/post studies or case series, and level 5 if gleaned from an observational report or case report involving a single subject or from clinical consensus.[20] We did not require a minimum sample size because of the relatively limited number of publications.

RESULTS

A total of 26 studies that met the criteria were identified and evaluated using either the PEDro evaluation tool, for RCTs, or the modified Downs and Black tool, for all other studies. Eight studies[7,22-28] addressed the pharmacologic management and 21 studies examined the nonpharmacologic management of OH (fluid and salt: n=3[7,26,28]; pressure devices: n=6[29-34]; FES: n=9[4,35-42]; exercise: n=3[43-45]; some studies address multiple treatments). One descriptive review on the nonpharmacologic management of OH after SCI was also found.[46]

Pharmacologic Management of Orthostatic Hypotension in Spinal Cord Injury

With the exception of 1 study (n=231),[7] the sample size for each of the studies was small (n=1–7) (table 1).[22-28]

Midodrine. Midodrine is a selective alpha-adrenergic agonist that exerts its actions via the activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and an elevation in blood pressure. The peak effect of midodrine is 25 to 30 minutes, with a half-life of about 3 to 4 hours. Usual doses are 2.5mg twice daily (at breakfast and lunch) or 3 times daily. Doses are increased quickly until a response occurs or a dose of 30mg/d is attained.[47] Midodrine does not cross the blood-brain barrier and is therefore not associated with central nervous system effects. The principal adverse effect of the peripherally acting alpha-1 agonists is vasoconstriction. Other adverse effects include uterine contractions; mydriasis; arterial hypertension, especially in the supine position; palpitations; tachycardia; and headaches.[48] However, the benefits of midodrine in the management of OH in subjects with SCI have been reported in a single level 2 RCT,[22] 2 level 4 studies,[23,24] and 1 level 5 study.[27]

Even though the only controlled trial consisted of just 4 subjects,[22] the study was a rigorous, double-blinded, placebo-controlled, randomized, crossover trial that included a within-subject design. Systolic blood pressure was increased during peak exercise (3 of 4 subjects), and exercise performance also was enhanced.

Fludrocortisone (Florinef). Fludrocortisone is a mineralocorticoid that stimulates the release of salt into the bloodstream. It increases blood volume and may enhance the sensi-

Table 1: Pharmacologic Management and Fluid and Salt Intake for the Management of Orthostatic Hypotension in Spinal Cord Injury

Author, Year; Country Score Research Design Total Sample Size	Methods	Outcome
Nieshoff et al,[22] 2004; USA PEDro=5 RCT N=4	Population: 4 patients with chronic, complete tetraplegia. Treatment: midodrine 5mg, 10mg, or placebo (unmarked capsule). Double-blind, placebo-controlled cross-over design. Outcome measures: measure of cardiovascular parameters during wheelchair ergometer test.	1. Midodrine 10mg elevated systolic blood pressure during exercise in 3 participants. Peak systolic blood pressure ranged from 90 to 126mmHg under baseline and placebo conditions, 114 to 148 after 5mg midodrine, and 104 to 200mmHg after 10mg. 2. Two participants demonstrated ↓perceived exertion and ↑oxygen uptake. 3. No adverse effects of midodrine.
Senard et al,[23] 1991; France Downs and Black score=11 Pre-post N=7	Population: 45-year-old man with chronic complete traumatic paraplegia; 6 male controls without SCI. Treatment: clonidine (150μg, twice daily) and midodrine (specific α 1-agonist; 10mg, twice daily). Heart rate assessed by blinded tester. Outcome measures: blood pressure, heart parameters, plasma catecholamine, α-adrenoceptor sensitivity.	1. The increase in systolic blood pressure induced by midodrine (10mg) was significantly higher in the patient (change of 56mmHg) than in controls (change of 15mmHg). 2. Midodrine and clonidine, either alone or in combination, led to increased resting blood pressure and decreased severity of OH.
Barber et al,[24] 2000; USA Downs and Black score=7 Case series N=2	Population: 2 patients with acute complete motor tetraplegia. Treatment: fludrocortisone acetate 0.1mg 4 times a day or midodrine 10mg 3 times a day. Outcome measures: blood pressure, heart rate, and symptoms of OH.	1. Fludrocortisone in both patients resulted in pitting edema of hands and lower limbs. No effect of fludrocortisone on OH. 2. Initiation of the midodrine resolved orthostatic symptoms in both subjects without any complications.
Frisbie and Steele,[7] 1997; USA Downs and Black score=18 Observational N=231	Population: SCI; ephedrine group: mean age, 57±15y, duration of paralysis 26±15y; no ephedrine group: mean age, 51±15.2y, 22±13.5y postinjury. Treatment: retrospective chart review of use of ephedrine (n=30), salt supplementation (n=6), fludrocortisone (n=3), or physical therapy. Outcome measures: OH symptoms, serum sodium, and urine osmolality.	1. Four patients on ephedrine commenced salt supplementation with meals and 3 of these because independent of ephedrine use. 2. Low blood sodium found in 54% of the patients with OH and 16% of those without; $P<.001$ (suggests salt supplementation may be an option for treatment). 3. Of 30 cases of subjects taking ephedrine, the authors state, "Although a single dose of ephedrine in the morning was usually sufficient, it was observed that some patients failed to recognize the need for a repeated dose of this medication later in the day."[p306]
Frisbie,[28] 2004; USA Downs and Black score=9 Observational N=4	Population: chronic, complete cervical tetraplegia; ASIA grade A. Treatment: evaluation of urinary salt and water output in relation to prescribed dose of ephedrine (dose range from 0 to 100mg daily). Outcome measures: severity of OH, urinary output.	1. With decreasing ephedrine dose (and OH severity), there was ↑mean daily output of urine sodium (50–181mEq), ↑ rate of creatinine secretion, ↑ rates of water excretion, ↓ urine osmolality, and ↑ sodium concentrations. 2. These results suggest that ephedrine can help to correct hyponatremia; however, renal conservation of water still exceeded that of sodium in 3 of the 4 patients. 3. Estimated daily intake of salt and water was inversely related to the ephedrine requirement, which suggests that greater salt and water intake may lead to more balanced renal action.
Mukand et al,[27] 2001; USA Downs and Black score=10 Case report N=1	Population: 21-year old man; SCI; traumatic; C6 tetraplegia; ASIA grade C, with symptomatic orthostatic hypotension. Treatment: Midodrine (2.5–15mg 3 times a day). Outcome measures: blood pressure, and symptoms of OH.	1. Gradual increase of midodrine dose from 2.5mg to 10mg (at 8:00 AM, 12:00 PM, and 4 PM) resulted in resolution of symptoms and orthostasis. Patient became able to participate fully in rehabilitation program.
Groomes and Huang,[25] 1991; USA Downs and Black score=9 Case report N=1	Population: 28-year-old with chronic C5 tetraplegia. Treatment: ergotamine (2mg), daily combined with fludrocortisone (.10–.05mg). Outcome measures: blood pressure.	1. After 10 days with fludrocortisone, patient able to tolerate sitting. After additional ergotamine, patient able to tolerate an upright position without symptoms.
Muneta et al,[26] 1992; Japan Downs and Black score=9 Case report N=1	Population: 72-year-old woman with nontraumatic SCI and paroxysmal hypotension. Treatment: several weeks of salt supplement (7 then 15g/d), followed by L-DOPS (100mg up to 600mg/d). Outcome measures: blood pressure, serum catecholamines, plasma renin activity.	1. After salt supplement, a marked ↑ in blood pressure and NE were observed in response to sitting; a decrease in basal plasma renin activity also was observed. 2. Addition of L-DOPS for 2 weeks resulted in a 5-fold to 10-fold elevation in catecholamines (epinephrine and NE) without any apparent increase in resting blood pressure. 3. Significant improvement in the symptoms of paroxysmal hypotension; patient became able to participate in rehabilitation program.

Abbreviations: ASIA, American Spinal Injury Association; NE, norepinephrine.

tivity of blood vessels to circulating catecholamines.[49,50] The starting dose is 0.1mg daily. Blood pressure rises gradually over several days, with a peak effect at 1 to 2 weeks. Doses should be adjusted at weekly or biweekly intervals. Hypokalemia (low potassium) occurs in 50% of subjects and hypomagnesemia in 5%. These may need to be corrected with supplements. Fludrocortisone should not be used in persons with congestive heart failure because of its marked effect on sodium retention. One level 4 case series,[24] 1 level 5 case report (n=1),[25] and 1 level 5 observational study[7] described its use in the treatment of OH within the SCI population.

Barber et al[24] found no effect of fludrocortisone on OH in 2 patients with SCI, while Groomes and Huang[25] found an improvement in 1 patient within 10 days of treatment. The other study, conducted by Frisbie and Steele,[7] combined fludrocortisone with other pharmacologic and physical agents in 3 patients; however, outcomes specific to this group were not described, so the specific effects of fludrocortisone cannot be discerned.

Dihydroergotamine. Dihydroergotamine and ergotamine both are ergot alkaloids that interact with alpha-adrenergic receptors and have selective vasoconstrictive effects on periph-

eral and cranial blood vessels. Peak plasma levels are reached about 2 hours after ingestion. In a single case report, ergotamine was combined with fludrocortisone to prevent symptomatic OH successfully in 1 subject with SCI.[25]

Ephedrine. Ephedrine is a nonselective alpha and beta receptor agonist with both central and peripheral action. The dose is 12.5 to 25mg orally 3 times a day. Side effects may include tachycardia, tremor, and supine hypertension. Ephedrine raises blood pressure, both by increasing cardiac output and by inducing peripheral vasoconstriction, and it has a plasma half-life ranging from 3 to 6 hours.[51] Evidence from 2 level 5 studies (retrospective chart reviews[7,28]) were found. Frisbie[28] reported that daily urinary output of salt and water was inversely related to the prescribed ephedrine dose in 4 patients with OH. These results suggest that ephedrine can help to correct hyponatremia; however, renal conservation of water still exceeded that of sodium in 3 of the 4 patients. In their observational study, Frisbie and Steele[7] reviewed 30 cases of subjects taking ephedrine and stated, "Although a single does of ephedrine in the morning was usually sufficient, it was observed that some patients failed to recognize the need for a repeated dose of this medication later in the day."(p306)

L-threo-3,4-dihydroxyphenylserine. L-DOPS is an exogenous, neutral amino acid, and a precursor of noradrenalin. Only 1 level 5 study has been published[26] evaluating the effects of L-DOPS on OH, and this was in a single patient with nontraumatic SCI. In this study, treatment with salt supplementation in combination with L-DOPS resulted in a marked reduction of syncopal attacks, decreased drowsiness associated with hypotension, and increased daily activity.

Pharmacologic Management Conclusions

There is level 2 evidence[22] that midodrine enhances exercise performance in some subjects with SCI, similar to other clinical populations with cardiovascular autonomic dysfunction. Nevertheless, it would be useful to confirm this evidence with a larger trial.

There is level 4 evidence,[24] based on a single case series involving 2 patients, that fludrocortisone is not effective for OH in patients with SCI. There is level 5 evidence[25] that daily ergotamine, combined with fludrocortisone, can successfully prevent symptomatic OH, but this is observed only in a single subject with SCI. There is level 5 evidence[7] that ephedrine reduces the likelihood of a patient experiencing hypotension. There is level 5 evidence,[26] based on the results of a single case study, that L-DOPS, in conjunction with salt supplementation, may be effective at reducing OH. Overall, for the studies assessing pharmacologic management of OH after SCI, the level of evidence ranges from level 2 to 5. Because there are few studies, all with very small sample sizes, it is clear that further research is necessary to confirm the benefits of these pharmacologic interventions for the treatment of OH.

Nonpharmacologic Management of Orthostatic Hypotension in Spinal Cord Injury

Of the nonpharmacologic studies, 3 involved the regulation of fluid and salt intake, while 18 addressed physical modalities, like abdominal binders, physical activity, and electrical muscle stimulation.

Fluid and Salt Intake for the Management of Orthostatic Hypotension in Spinal Cord Injury

OH is common among persons with tetraplegia and high paraplegia, in whom symptoms are variable, and abnormal salt and water metabolism often coexist (table 1). Increases in fluid intake and a high salt diet can expand extracellular fluid volume and augment orthostatic responses. This simple intervention appears to be effective in patients with idiopathic OH without SCI.[52,53] Frisbie and Steele[7] reported that 3 of their 4 subjects taking salt supplementation were able to become independent of the use of ephedrine. Frisbie[28] further showed that the estimated daily intake of salt and water was inversely related to the ephedrine requirement in 4 patients with OH, and suggested that greater salt and water intake may lead to more balanced renal action.

Effect of Pressure Interventions in the Management of Orthostatic Hypotension in Spinal Cord Injury

The application of external counter-pressure by means of devices like abdominal binders or pressure stockings is thought to decrease capacitance within the lower extremity and abdominal vasculature beds, which are major areas of blood pooling during standing (table 2). The studies examining pressure interventions in patients with SCI generally have used a crossover design to test different pressure conditions within the same group of participants (eg, with and without stockings) in either a random[29,33] or nonrandom order.[31,32,34]

Because the studies did not assess the effects resulting from continued use, long-term outcomes are uncertain, as are the outcomes resulting from pressure removal after extended use. The application of these interventions must therefore be interpreted with caution. Among 6 wheelchair athletes with paraplegia, Kerk et al[32] found no statistically significant effects of an abdominal binder used in the sitting position on any cardiovascular or kinematic variables at either submaximal or maximal levels of exercise. Similarly, in his review, Bhambhani[54] concluded that the use of abdominal binders in patients with SCI does not influence cardiovascular physiologic responses. Huang et al[33] similarly reported that the use of assistive compressive devices (inflatable abdominal corset, pneumatic leg splints) do not improve pulmonary ventilatory parameters during postural change. On the other hand, in a small group of 9 subjects with SCI,[30] stockings and an abdominal binder did decrease heart rate by 5 beats a minute and increase stroke volume by 13mL/beat during submaximal upper-extremity exercises, but not during maximal exercises.[29] In their study, Vallbona et al[34] observed a drop in systolic and diastolic blood pressure during passive tilt in patients with tetraplegia and, in contrast, an increase in diastolic blood pressure among patients with paraplegia. Krassioukov and Harkema[31] found that using a harness (which applies abdominal pressure) during locomotor training increased diastolic blood pressure in those with SCI, but not in able-bodied patients.

Effect of Functional Electrical Stimulation on Orthostatic Hypotension in Spinal Cord Injury

The application of FES activates the physiologic muscle pump via intermittent muscle contractions around both the superficial and the deep veins of the legs, thereby facilitating venous blood return (table 3). Several studies have demonstrated that FES-induced contractions of the leg muscles increase cardiac output and stroke volume, effects that are attributable to increased venous return.[36,42] The increases in ventricular filling and left ventricular end-diastolic volume may generate greater cardiac output and, as such, an increase in arterial blood pressure. Therefore, FES-induced contraction of the leg muscles may attenuate the drop in systolic blood pressure that occurs in patients with SCI in response to an orthostatic challenge, and may artificially restore the body's ability to return blood from below the level of the lesion back to the

Table 2: Pressure Interventions for Management of Orthostatic Hypotension in Spinal Cord Injury

Author, Year; Country Score Research Design Total Sample Size	Methods	Outcome
Hopman et al,[29] 1998; USA PEDro=5 RCT N=9	Population: 9 males: 5 with tetraplegia, 4 with paraplegia; 8 complete, 1 incomplete. Treatment: 5 discontinuous maximal arm ergometer tests on different days while (1) sitting, (2) supine, (3) sitting plus an anti-gravity suit, (4) sitting plus stockings and an abdominal binder, and (5) sitting plus FES of the leg muscles. Outcome measures: oxygen uptake, carbon dioxide output, respiratory parameters, heart rate, blood pressure.	1. Supine posture increased peak oxygen uptake in tetraplegia, but reduced heart rate in paraplegia compared to sitting. 2. There was no effect of the anti-G suit, stockings plus abdominal binder, or FES on oxygen uptake, heart rate, ventilatory exchange, or power output. The anti-G suit did significantly reduce perceived exertion among subjects with tetraplegia only. 3. Results suggest that there are no hemodynamic benefits of stockings, abdominal binders, or FES in these patients.
Hopman et al,[30] 1998; Netherlands PEDro=5 RCT N=9	Population: 5 with tetraplegia, 4 with paraplegia (same subjects as Hopman et al[29]). Treatment: 5 conditions as in Hopman et al,[29] except submaximal exercise at 20%, 40%, and 60% maximum power output. Outcome measures: oxygen uptake, carbon dioxide output, respiratory parameters, heart rate, blood pressure.	1. Tetraplegia: ↑ oxygen uptake, cardiac output, stroke volume, blood pressure, and stroke volume with FES; ↑ cardiac output, ↑ stroke volume, and ↓ heart rate with binders and stockings; ↓ heart rate and ↑ blood pressure with anti-G suit. 2. Paraplegia: ↑ oxygen uptake and ↓ heart rate with FES; ↓ oxygen uptake and ↓ heart rate with anti-G suit; ↓ oxygen uptake with stockings and binders.
Huang et al,[33] 1983; USA PEDro=5 RCT N=27	Population: 27 with tetraplegia; C4–C7; age 17–69y; mean of 47d postinjury; none had motor function, some had slight sensory sparing in the sacral segments. Treatment: inflatable abdominal corset and bilateral pneumatic leg splints. Outcome measures: respiratory rate, tidal volume, heart rate, SBP, DBP.	1. The use of assistive compressive devices does not improve pulmonary ventilatory parameters during postural change. 2. Assistive devices had no effect on SBP except in the 20° and 45° head-up positions ($P<.01$). In the 45° position, abdominal corset was significantly better than pneumatic leg splints at maintaining SBP. Same trend for DBP. 3. Both devices failed to influence heart rate ↓ with 20° head-down position. There was a significant effect of assistive devices on heart rate ↑ in the 20° and 45° head-up positions ($P<.01$).
Krassioukov and Harkema,[31] 2006; Canada Downs and Black score=17 Prospective controlled trial N=20	Population: 6 with complete tetraplegia, 5 with complete paraplegia, ASIA grade A; 9 able-bodied controls. Treatment: with and without harness for locomotor training while supine, sitting, and standing (within-subject analysis). Outcome measures: blood pressure, heart rate.	1. Orthostatic stress significantly decreased arterial blood pressure only in subjects with cervical SCI ($P<.05$). 2. Harness application had no effect on cardiovascular parameters in able-bodied subjects, whereas DBP was significantly increased in those with SCI. 3. Orthostatic changes in cervical SCI when sitting were ameliorated by harness application. However, while standing with harness, subjects with cervical SCI still developed orthostatic hypotension.
Kerk et al,[32] 1995; USA Downs and Black score=13 Prospective controlled trial N=6	Population: chronic complete paraplegia. Treatment: cross-over design: abdominal binder (experimental group) versus no abdominal binder (controls). Outcome measures: blood pressure, heart rate, maximum oxygen consumption, respiratory parameters, and wheelchair propulsion.	1. Five of 6 subjects demonstrated a mean increase of 31% in forced vital capacity with binder, compared to without. No statistical significance, but this may be because the sixth subject experienced an 18% decrease in forced vital capacity when wearing the binder.
Vallbona et al,[34] 1963; USA Downs and Black score=13 Pre-post N=17	Population: 12 males with tetraplegia, 5 males and females with paraplegia, ages 16 to 43 years, 3–48mo postinjury Treatment: pressure suit (CSU-3/P antigravity suit) inflated to a pressure of plus 30cm water. Outcome measures: presence of symptoms, heart rate, SBP and DBP during passive tilting (with feet down) on a motorized tilt table.	1. Presence of the suit attenuated the increase in heart rate ($P>.20$; not significant) and drop in SBP and DBP ($P<.005$; significant) during passive tilt in patients with tetraplegia. 2. In terms of heart rate and SBP, patients with paraplegia responded to passive tilting in a pressure suit similarly to passive tilting without the suit. However, an increase in DBP comparable to that of subjects with tetraplegia wearing pressure suits was observed.

Abbreviations: ASIA, American Spinal Injury Association; DBP, diastolic blood pressure; SBP, systolic blood pressure.

heart. In fact, FES may be effective during an orthostatic challenge by redistributing blood volume from the regions of the body that are below the level of the SCI.[40] FES of leg muscles was shown to increase cardiac output and stroke volume in 6 men with paraplegia while performing arm-crank exercise at maximal effort. These results suggest that FES of leg muscles may alleviate the lower-limb pooling that occurs during an orthostatic challenge. FES results in a dose-dependent increase in blood pressure, independent of the stimulation site, so it may be useful in treating OH.[37]

FES may be an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in subjects with SCI. Three level 2 RCTs[35-37] and 6 nonrandomized trials[4,38-42] provide support for the use of FES in subjects with SCI. FES may permit people with tetraplegia to experience smaller hemodynamic changes with changes in posture, and consequently to stand up more frequently and for longer durations.[35,37] This effect may be more beneficial to those subjects with tetraplegia who have a compromised autonomic nervous system and may not be able to adjust hemodynamically to changes in position.[4]

Effects of Exercise on Orthostatic Hypotension in Spinal Cord Injury

After exercise, patients with SCI may exhibit positive changes in the autonomic regulation of their cardiovascular systems (table 4).[43] Exercise or even passive movement of the legs has the potential to stabilize the reduced central blood volume that occurs in patients with SCI during an orthostatic challenge. For example, Dela et al[55] noted a pronounced

Table 3: Functional Electrical Stimulation on Orthostatic Hypotension in Spinal Cord Injury

Author, Year; Country Score Research Design Total Sample Size	Methods	Outcome
Elokda et al,[35] 2000; USA PEDro=5 RCT N=5	Population: 2 with tetraplegia, 3 with paraplegia, all complete, in acute period, 2–4wk post-SCI. Treatment: tilt table, 6min at each tilt angle (0°, 15°, 30°, 45°, 60°), with 4min of recovery between each, with or without bilateral ankle plantar flexor and knee extensor electrical stimulation. Application order or absence of FNS was counterbalanced. Outcome measures: heart rate, blood pressure, perceived exertion.	1. At tilt angles of 15°, 30°, 45°, and 60°, SBP was significantly lower when FNS was not applied compared with when it was administered, and the difference was more marked with increasing tilt angles. 2. There was a progressive decrease in blood pressures with increasing tilt angle, with this decrease less pronounced in the FNS condition. 3. *Post hoc* analysis showed that heart rate was significantly higher with vs without FNS at 60° tilt.
Faghri and Yount,[36] 2002; USA PEDro=5 RCT N=29 (14 SCI)	Population: 7 with paraplegia, 7 with tetraplegia; 4 incomplete, 10 complete; able-bodied, n=15. Treatment: random order of standing with or without FES (30min) for subjects with SCI; voluntary tiptoe contractions during 30min standing for able-bodied subjects. Outcome measures: hemodynamic parameters while supine-sitting-30min standing.	1. Reductions ($P<.05$) of up to 10% blood pressure for subjects with SCI from sitting to passive standing, but minimal changes when moving to FES standing. 2. After 30min passive standing (no FES), there was a reduction in stroke volume and cardiac output. After 30min FES standing, prestanding hemodynamics were maintained, except for a significant reduction in stroke volume.
Sampson et al,[37] 2000; USA PEDro=5 RCT N=6	Population: complete motor SCI (lesions above T6); 3 with recent injury, 3 with long-standing injury. Treatment: with and without lower-extremity FES while tilted in 10° increments every 3min, from 0° to 90° with varying intensities of stimulation. Outcome measures: blood pressure, heart rate, perceived syncope score.	1. ↑ Heart rate in both groups with ↑ incline angle. Mean DBP was lower in subjects with recent (105mmHg) versus long-standing SCI (123mmHg). 2. ↑ SBP and DBP with ↑ stimulation intensities and ↓ blood pressure with ↑ incline angle ($P<.001$) regardless of the site of stimulation. 3. Subjects tolerated higher angles of incline with FES than without. The higher the intensity of FES, regardless of the stimulation site, the greater the tilt incline tolerated.
Faghri et al,[4] 2001; USA Downs and Black score=22 Prospective controlled trial N=14	Population: 7 with tetraplegia, 7 with paraplegia; 4 incomplete, 10 complete. Treatment: FES-augmented standing (active) and non-FES standing (passive), for 30min; tests were separated by at least 24h. Outcome measures: hemodynamic parameters.	1. Blood pressure changed 8% to 9% when moving from sitting to passive standing (no FES). The augmented FES condition prevented blood pressure change when moving from sitting to standing.
Raymond et al,[38] 2002; Australia Downs and Black score=16 Prospective controlled trial N=16 (8 SCI)	Population: 8 males with complete paraplegia, 8 male able-bodied controls. Treatment: LBNP was used to provide the orthostatic challenge. Subjects were evaluated (1) during supine rest, (2) supine with submaximal ACE, (3) ACE+LBNP, and (4) for SCI only, ACE+LBNP+leg ES. Outcome measures: heart rate, stroke volume, cardiac output.	1. ES increased stroke volume from ACE+LBNP to ACE+LBNP+ES for both SCI and able-bodied groups; ES did not affect oxygen uptake or cardiac output.
Raymond et al,[42] 1999; Australia Downs & Black score=10 Prospective controlled trial N = 16 (8 SCI)	Population: 8 males with complete paraplegia, T5–T12, mean age, 41.3±6.5y, >3y postinjury; 8 able-bodied controls. Treatment: ES-induced leg muscle contractions during orthostatic challenge to examine the effects on venous pooling. Outcome measures: heart rate, SV, Q, SBP, DBP, MAP, limb volumes, $\dot{V}O_2$.	1. During orthostatic challenge, heart rate and $\dot{V}O_2$ did not differ significantly with ES compared to without ES. 2. ES during orthostatic challenge augmented SV by 13mL/beat compared to without ES; Q increased by 0.7L/min. SBP, DBP, or MAP with ES did not change significantly. 3. ES elicited a significant reduction in calf volume during orthostatic challenge. 4. Even modest levels of ES provide a role in the assistance of blood redistribution from the lower limbs.
Faghri et al,[39] 1992; USA Downs & Black score=14 Pre-post N=13	Population: 6 with paraplegia (T4–T10); 7 with tetraplegia (C4–C7). Treatment: FES-leg cycle ergometer training, 3 times a week, for about 12wk (36 sessions). Outcome measures: $\dot{V}O_2$, $\dot{V}E$, RER, blood pressure, heart rate, SV, and Q.	1. After training, ↑ resting heart rate and SBP in subjects with tetraplegia and ↓ systolic and diastolic blood pressure in subjects with paraplegia. 2. In both groups, heart rate and blood pressure during submaximal exercise significantly decreased, and stroke volume and cardiac output significantly increased after program. 3. These results suggest that FES-LCE training improves peripheral muscular and central cardiovascular fitness in subjects with SCI.
Davis et al,[40] 1990; USA Downs & Black score=16 Pre-post N=12	Population: 12 males with paraplegia (T5–L2); FES group, n=6; no FES (control) group, n=6. Treatment: submaximal and maximal ACE with or without FES of paralyzed leg muscles. Outcome measures: peak $\dot{V}O_2$, $\dot{V}E$, perceived exertion RER, blood pressure, heart rate, resting SV and Q, total peripheral resistance.	1. No significant differences between the FES and control groups in terms of peak $\dot{V}O_2$(2.09L/min), maximal heart rate, $\dot{V}E$, RER, or perceived exertion. 2. No differences in power output or $\dot{V}O_2$ during peripheral FES application, but stroke volume and Q were higher during the FNS- induced leg contractions. Neither rest nor exercise heart rate was significantly influenced by lower limb FES in the FES group. 3. Heart rate, SV, and Q were not significantly altered at rest or during hybrid exercise in controls. There was a decrease in the peripheral and overall ratings of perceived exertion. 4. No changes in blood pressure, impedance indexes of myocardial contractility, or differentiated subjective ratings of perceived exertion during hybrid exercise vs non-FES conditions.
Chao and Cheing,[41] 2005; China Downs & Black score=15 Post N=16	Population: complete motor tetraplegia. Treatment: progressive head-up tilting maneuver with and without FES applied to 4 muscle groups. Outcome measures: blood pressure, heart rate, perceived presyncope score.	1. With increasing tilt angle, ↓ SBP and DBP and ↑ heart rate with and without FES. 2. Adding FES to tilting significantly attenuated the drop in SBP by 3.7±1.1mmHg ($P=.005$), the drop in DBP by 2.3±0.9mmHg ($P=.018$), and the heart rate increase by 1.0±0.5beats/min ($P=.039$) for every 15° increment in the tilt angle. 3. FES increased the overall mean standing time by 14.3±3.9min ($P=.003$).

Abbreviations: ACE, arm crank exercise; DBP, diastolic blood pressure; ES, electrical stimulation; FNS, functional neuromuscular stimulation; LBNP, lower-body negative pressure; LCE, leg cycle ergometer; MAP, mean arterial pressure; Q, cardiac output; RER, respiratory exchange ratio; SBP, systolic blood pressure; SV, stroke volume; $\dot{V}E$, expired volume per unit time; $\dot{V}O_2$, oxygen consumption per unit time.

Table 4: Exercise for Orthostatic Hypotension in Spinal Cord Injury

Author, Year; Country Score Research Design Total Sample Size	Methods	Outcome
Lopes et al,[43] 1984; USA PEDro=2 RCT N=12 (6 SCI)	Population: 5 with tetraplegia, 1 with paraplegia; 6 control subjects. Treatment: random assignment to active exercise (60 bilateral forearm flexion and extension movements a minute during the first and third minute of each tilt angle) vs no upper limb exercises during tilt from 0° to 70° by 10° increments at 5-min intervals until blood pressure dropped below 70/40. Outcome measures: blood pressure, symptoms of hypotension.	1. No significant difference between the active upper-extremity exercise group versus the nonexercise group with respect to tolerance to progressive vertical tilt.
Engelke et al,[45] 1994; USA Downs and Black score=10 Prospective controlled trial N=10	Population: 10 sedentary subjects with paraplegia, T1–T12, age 36±4y, 118±21mo wheelchair use. Treatment: maximal arm-crank exercise. Outcome measures: blood pressure, heart rate, forearm vascular resistance, and vasoactive hormone responses before and during 15 minutes of 70° HUT).	1. Heart rate increased similarly in the control and postexercise conditions. 2. Reduction in SBP was significantly larger during HUT before than after arm-crank exercises (–12.0±4.6mmHg vs –0.3±4.3mmHg). 3. Postexercise increase in FVR from supine to HUT was significantly greater than increase observed in control condition. 4. Carotid-cardiac baroreflex also increased significantly after exercise. 5. No difference in vasoactive hormone responses between the 2 conditions. 6. No difference in either leg compliance or plasma volume between the 2 conditions.
Ditor et al,[44] 2005; Canada Downs and Black score=18 Pre-post N=8	Population: sensory incomplete cervical SCI; level of injury C4–C5; ASIA grades B and C. Treatment: 6mo BWSTT. Outcomes measures: heart rate, blood pressure, and orthostatic responses, heart rate variability.	1. ↓ Resting heart rate, but no change in blood pressure after BWSTT. 1. No effect on blood pressure or heart rate during the 60° Head Up Test. 2. A trend (P=.09) toward a relative exaggeration of the pressor response to orthostatic stress during the tilt test (measured by ↓ low frequency power of heart rate), suggesting improved orthostatic tolerance.

Abbreviations: ASIA, American Spinal Injury Association; BWSTT, body weight-supported treadmill training; FVR, forearm vascular resistance; HUT, head-up tilt.

increase in blood pressure in subjects with tetraplegia when their legs were passively moved with a cycle ergometer. There also is some evidence that exercise training can enhance sympathetic outflow in patients with SCI, as shown by an increase in catecholamine response to maximal arm ergometry exercises.[56] To date, only 3 studies have attempted to assess the effects of exercise on OH in patients with SCI. Lopes et al[43] identified no treatment effect of exercise on orthostatic tolerance when patients performed upper-extremity exercises during a progressive vertical tilt protocol predominantly in subjects with tetraplegia. In contrast, Engelke et al[45] found a bout of maximal arm-crank exercise did reduce the orthostatic hypotension in subjects with paraplegia during an orthostatic challenge given 24 hours after the exercise bout. It is likely that the differences in results are in part a result of the level of paralysis. Ditor et al[44] demonstrated that 6 months of body weight support treadmill training did not improve orthostatic tolerance in a population of persons with sensory-incomplete cervical SCI (C4–C5). Nonetheless, the authors found their results encouraging, because they suggest that orthostatic tolerance is retained after exercise training.

Nonpharmacologic Management Conclusions

Level 5 evidence exists from 2 observational studies[7,28] to suggest that salt and fluid regulation, in combination with other pharmacologic interventions, may reduce the symptoms of OH. However, these conclusions should be interpreted with caution, because no evidence exists on the effect of salt or fluid regulation alone in the management of OH in patients with SCI. Currently, guidelines that suggest appropriate water and salt intake specific to patients with SCI do not exist. There is level 2 evidence from a single lower-quality RCT that pressure from elastic stockings and abdominal binders may improve cardiovascular physiologic responses during submaximal, but not maximal, upper-extremity exercises. However, other studies have generated evidence that contradicts this. There is also level 2 evidence from small, lower-quality RCTs[35-37] that FES is an important treatment adjunct to minimize cardiovascular

changes during postural orthostatic stress in subjects with SCI. Level 2 evidence exists that simultaneous upper-extremity exercises may increase orthostatic tolerance during a progressive tilt exercise in subjects with paraplegia,[45] but not tetraplegia.[43] In addition, level 4 evidence[44] exists that 6 months of body weight support treadmill training does not substantially improve orthostatic tolerance during a tilt test.

DISCUSSION

A systematic review of the literature found 26 articles evaluating pharmacologic and nonpharmacologic (fluid salt intake, pressure interventions, FES, exercise) interventions (with some studies applying more than 1 of these interventions) for the management of OH in persons with SCI. Overall, the quality of the literature was poor. The pharmacologic interventions included 1 fair-quality RCT (using midodrine) with a PEDro score of 5 of a maximum 10. The rest of the pharmacologic studies were of low quality with an average Downs and Black Score of 10 of a possible 28, and were primarily case series using retrospective data collected from a chart review. Similarly, the nonpharmacologic RCTs had an average PEDro of 5 of 10, and the nonrandomized trials had an average of 14 of 28.

Despite the fact that a wide array of physical and pharmacologic measures have been recommended for the general management of OH,[17] very few have been rigorously evaluated for use in SCI. Of the pharmacologic interventions, only for minodrine is there supportive evidence from a low-quality RCT (level 2 evidence). Furthermore, the studies addressing the pharmacologic management of OH after SCI are few in number and small in terms of sample size, most involving 1 to a few subjects. Another problem with the literature involves combination therapies, because it invariably is difficult to determine the effects of 1 medication when it is combined with others. Nonetheless, it is reasonable to state that if nonpharmacologic methods to manage OH fail, midodrine might be considered for the management of OH in persons with SCI, given its level 2 evidence. Clearly, further research is necessary to confirm any beneficial effect midodrine has, and to assess the potential role of numerous other pharmacologic interventions that have been demonstrated to be efficacious for treatment of OH in other conditions of orthostatic intolerance.

FES is one of the only nonpharmacologic interventions that has some evidence (level 2) to support its utility. The use of FES has been reported to be beneficial during the acute phase of SCI in improving orthostatic tolerance during postural training, but retention and habituation of these effects are unknown. For example, it is unknown whether muscle fatigue or habituation from the stimulation reduces the potential for longer use. Similarly, after repeated bouts of FES, the potential retention of the vascular benefits are unknown. Future research to address these gaps would provide valuable insight. More research is also required to determine the feasibility and practicality of FES to reduce the effects of OH. In a review of nonpharmacologic interventions for OH post-SCI, Gillis et al[46] stated that "FES of the legs holds the most promise"(p652) with an approximate 8/4mmHg reduction in blood pressure fall during an orthostatic challenge.

CONCLUSIONS

Although a wide array of physical and pharmacologic measures are recommended for the general management of OH, very few have been evaluated for use in SCI. Because the mechanisms of OH are different in SCI than in other conditions, further research needs to quantify the treatments for OH in patients with SCI, especially the many other pharmacologic interventions that have been shown to be effective in non-SCI conditions.

APPENDIX 1: SIGNS AND SYMPTOMS OF ORTHOSTATIC HYPOTENSION

- Light-headedness
- Dizziness
- Fainting
- Blurred vision
- Fatigue
- Muscle weakness
- Syncope (temporary loss of consciousness)

APPENDIX 2: FACTORS PREDISPOSING TO ORTHOSTATIC HYPOTENSION AFTER SPINAL CORD INJURY

- Multifactorial[5]
- Loss of tonic sympathetic control[56,57]
- Altered baroreceptor sensitivity[58,59]
- Lack of skeletal muscle pumps[10,36,38]
- Cardiovascular deconditioning[11,60]
- Altered salt and water balance[28]

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