

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

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Abstract

OBJECTIVE—To systematically review the evidence for the management of orthostatic hypotension (OH) in individuals with spinal cord injuries (SCI).

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, so as 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 pharmacological and non-pharmacological intervention for the management of OH in individuals with SCI.

DATA EXTRACTION—Two independent reviewers evaluated the quality of each study, using the PEDro score for randomized controlled trials (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 pharmacological and 21 non-pharmacological studies were identified which met the criteria. Of these 26 studies (some include both pharmacological and non-pharmacological interventions), only one pharmacological RCT was identified (low quality RCT producing Level 2 evidence), in which midodrine was found to be effective in the management of

OH following SCI. Functional electrical stimulation (FES) was one of the only non-pharmacological interventions with some evidence (Level 2) to support its utility.

CONCLUSIONS—Although a wide array of physical and pharmacological 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 individuals with SCI, especially of the many other pharmacological interventions which have been shown to be effective in non-SCI population.

Keywords

spinal cord injuries; orthostatic hypotension; treatment; therapy; review

Introduction

The definition of orthostatic hypotension (OH) 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, upon changing body position from a supine position to an upright posture, regardless of the presence of symptoms. Numerous studies have documented the presence of OH following spinal cord injury (SCI).—, 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. Not only is this condition evident in the acute period post-injury, it has persisted in a significant number of individuals for many years.— Standard mobilization during physiotherapy (e.g., sitting or standing) is reported to induce blood pressure decreases that are diagnostic of OH in 74% of SCI patients, and which are accompanied by OH symptoms (like light-headedness or dizziness, Table 1) in 59% of SCI individuals. This, in turn, may have a negative impact upon the ability of SCI individuals to participate in rehabilitation. Current management approaches for the treatment of OH consists of pharmacological and non-pharmacological interventions.

The low level of efferent sympathetic nervous activity and the loss of reflex vasoconstriction following SCI are among the major causes of OH. The decrease in arterial blood pressure following a change to an upright position in individuals with SCI appears to be related to excessive pooling of blood in the abdominal viscera and lower extremities., , The excessive venous pooling in the lower extremities, and the reduced blood volume in the intra-thoracic veins, ultimately lead to a decrease in end-diastolic volume, and thus a decrease in left ventricular stroke volume. 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 in a reduction in cerebral flow, which presents as the signs and symptoms of OH (Table 1).

In addition to central causes of OH following SCI, there also is some evidence suggesting that changes in the periphery, such as up-regulation of the potent vasodilator, nitric oxide (NO), might contribute to orthostatic intolerance in this population. In experimental animals, it has been demonstrated that NO synthase expression is dysregulated following SCI.

Furthermore, Wecht and co-investigators found that intravenous infusion of NO synthase inhibitors facilitates the normalization of blood pressure in individuals with SCI.

Several other factors may predispose spinal cord-injured individuals to OH including: low plasma volume; hyponatremia; and cardiovascular de-conditioning due to prolonged bed-rest (Table 2)., , As well, the prevalence of OH is more common in tetraplegia,, , and in individuals who have sustained a traumatic SCI versus those whose cord damage has been non-traumatic, as with cervical spine stenosis.

The majority of our understanding of the pathophysiology and management of OH is derived from the management of this condition in individuals with central autonomic neurodegenerative disorders (e.g. multiple system atrophy, Parkinson's disease), and patients with peripheral autonomic disorders (e.g. autonomic peripheral neuropathies, pure autonomic failure)., From previous studies in non-SCI individuals, it is well established that a combination of patient education and the use of pharmacological and non-pharmacological 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. The deleterious effects of low blood pressure such as a greater risk of developing pressure ulcers as a result of reduced tissue perfusion, and an increased dependence on the renin-angiotension system, as a result of renal hypoperfusion, provide reasons to consider normalizing blood pressure independent of OH symptoms, however, the current general approach in the management of OH is to implement therapeutic interventions in stages, dependent upon the severity of symptoms. It is well known from previous studies in non-SCI populations that non-pharmacological measures alone often are insufficient to render OH asymptomatic. However, given that the mechanisms of OH development appear to be different in individuals with SCI, it is important to assess the effectiveness of treatment strategies specific to individuals 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 www.scireproject.com.

Methods

A keyword 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 of spinal cord injury, paraplegia and tetraplegia were individually paired with orthostatic hypotension, orthostatic intolerance, and blood pressure. Studies which did not have outcomes evaluating OH - like blood pressure or OH symptoms (e.g., light-headedness, dizziness) - were excluded.

The quality of each study was scored by two independent reviewers. The 11-item Physiotherapy Evidence Database (PEDro) was used to score randomized controlled trials. Note that question 1 (external validity whether eligibility criteria was specified) is not part of

the final score. The PEDro score comprises questions 2 through 11 which address internal validity (e.g., blinding of assessors) with higher scores (maximum 10) indicating better methodological quality (9–10: excellent; 6–8: good; 4–5: fair; <4: poor. A modified version of the Downs and Black evaluation tool 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.

Sackett's description of levels of evidence was used to draw conclusions about the level of evidence for the accumulated studies. Sackett's Levels of Evidence were collapsed into 5 categories, whereby evidence was rated 'Level 1' if derived from 'good' to 'excellent' RCTs with PEDro scores ≥ 6 ; 'Level 2' if derived from RCTs with PEDro scores ≥ 5 or from non-randomized 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. We did not require a minimum sample size, due to 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, – addressed the pharmacological management and 21 studies examined the non-pharmacological management of OH (fluid and salt: n=3, , ; pressure devices: n=6–; functional electrical stimulation (FES) n=9, –; and exercise, n=3–) (note, some studies address multiple treatments). One descriptive review on the non-pharmacological management of orthostatic hypotension after spinal cord injury was also found.

Pharmacological Management of OH in SCI (Table 3)

With the exception of one study (n=231) , the sample size for each of the studies was small (n=1 to 7). –

Midodrine is a selective alpha-adrenergic agonist, which 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 25–30 min with half-life of about 3 to 4 hours. Usual doses are 2.5mg twice daily (at breakfast and lunch) or three times daily. Doses are increased quickly until a response occurs or a dose of 30 mg/day is attained. Midodrine does not cross the blood-brain barrier and is, therefore, not associated with CNS 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 lying position, palpitations, tachycardia and headaches. The benefits of midodrine however, in the management of OH in individuals with SCI have been reported in a single Level 2 RCT , two Level 4 studies, , and one Level 5 study.

Even though the only controlled trial consisted of just 4 subjects, the study was a rigorous, double-blinded, placebo-controlled, randomized, cross-over trial which included within-subjects design. Not only was systolic blood pressure increased during peak exercise (3/4 subjects), but exercise performance also was enhanced.

Fludrocortisone (Florinef) is a mineralocorticoid which stimulates the release of salt into the bloodstream. It increases blood volume and may enhance the sensitivity of blood vessels to circulating catecholamines. The starting dose is 0.1 mg daily. Blood pressure rises gradually over several days, with a peak effect at 1–2 weeks. Doses should be adjusted at weekly or biweekly intervals. Hypokalemia (low potassium) occurs in 50% of individuals, 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, one Level 5 case report (n=1), and one Level 5 observational study described its use in the treatment of OH within the SCI population.

Barber et al. found no effect of fludrocortisone on OH in two patients with SCI, while Grooms et al. found an improvement in one patient within 10 days of treatment. The other study, conducted by Frisbie and Steele, combined fludrocortisone with other pharmacological and physical agents in three patients; however, outcomes specific to this group were not described, so that the specific effects of fludrocortisone cannot be discerned.

Dihydroergotamine and ergotamine both are ergot alkaloids which interact with alpha adrenergic receptors and have selective vasoconstrictive effects on peripheral 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 successfully prevent symptomatic OH in one individual with SCI.

Ephedrine is a non-selective, alpha and beta receptor agonist, with both central and peripheral action. The dose is 12.5 to 25 mg orally 3 times per day. Side effects may include tachycardia, tremor and supine hypertension. Ephedrine raises blood pressure, both by increasing cardiac output and inducing peripheral vasoconstriction, and it has a plasma half-life ranging from 3 to 6 hours. Evidence from two Level 5 studies (retrospective chart reviews) were found. Frisbie 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 reviewed 30 cases of subjects taking ephedrine and stated “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.”

L-threo-3,4-dihydroxyphenylserine (L-DOPS) is an exogenous, neutral amino acid, and a precursor of noradrenalin. Only one Level 5 study has been published evaluating the effects of L-DOPS on OH, and this was in a single patient with non-traumatic 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 that midodrine enhances exercise performance in some individuals 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, based upon a single case series involving two patients, that fludrocortisone is not effective for OH in patients with SCI. There is Level 5 evidence that daily ergotamine, combined with fludrocortisone, can successfully prevent symptomatic OH; but, this is only observed in a single individual with SCI. There is Level 5 evidence that ephedrine reduces the likelihood of a patient experiencing hypotension. There is Level 5 evidence, based upon the results of a single case study, that L-DOPS, in conjunction with salt supplementation, may be effective at reducing OH.

Non-pharmacological Management of OH in SCI

Of the non-pharmacological studies, three 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 OH in SCI (Table 3)

OH is common among persons with tetraplegia and high paraplegia, in whom symptoms are variable, and abnormal salt and water metabolism often coexist. 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., Frisbie and Steele reported that 3 of their 4 subjects taking salt supplementation were able to become independent of the use of ephedrine. Frisbie 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 OH in SCI (Table 4)

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. The studies examining pressure interventions in SCI patients generally have utilized a cross-over design to test different pressure conditions within the same group of individuals (e.g., with and without stockings), in either a random, or non-random order., ,

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 paraplegic wheelchair athletes, Kerk et al. found no statistically significant effects of an abdominal binder used in the sitting position on any cardiovascular or kinematic variables at either sub-maximal or maximal levels of exercise. Similarly, in his review, Bhambhani concluded that the use of abdominal binders in SCI patients does not influence

cardiovascular physiological responses. Huang et al. similarly reported that the use of assistive compressive devices (inflatable abdominal corset and pneumatic leg splints) do not improve pulmonary ventilatory parameters during postural change. On the other hand, in a small group of 9 SCI subjects, stockings and an abdominal binder did decrease heart rate by 5 beats/min and increase stroke volume by 13 ml/beat during sub-maximal upper extremity exercises, but not during maximal exercises. In their study, Vallbona et al. 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 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 individuals.

Effect of Functional Electrical Stimulation (FES) on OH in SCI (Table 5)

The application of FES activates the physiologic muscle pump via intermittent muscle contractions around both the superficial and deep veins of the legs, thereby facilitating venous blood return. Several studies have demonstrated that FES-induced contractions of the leg muscles increases cardiac output and stroke volume, effects that are attributable to increased venous return. 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 BP that occurs in SCI patients 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 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. 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 that it may be useful in treating OH.

FES may be an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in individuals with SCI. Three Level 2 RCTs– and six non-randomized trials,, – provide support for the use of FES in individuals 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. 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.

Effects of Exercise on OH in SCI (Table 6)

Following exercise, individuals with SCI may exhibit positive changes in the autonomic regulation of their cardiovascular system. Exercise or even passive movement of the legs has the potential to stabilize the reduced central blood volume that occurs in individuals with SCI during an orthostatic challenge. For example, Dela et al. noted a pronounced increase in blood pressure in individuals 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 individuals with SCI, as shown by an increase in catecholamine response to maximal arm ergometry exercises. To date, only three studies have attempted to assess the effects of exercise on OH in SCI patients. Lopes et al. identified no treatment effect of exercise on orthostatic tolerance, when patients performed upper extremity exercises during a progressive vertical tilt protocol predominantly in individuals with tetraplegia. In contrast, Engelke et al. found a bout of maximal arm-crank exercise did reduce the orthostatic hypotension in individuals with paraplegia during an orthostatic challenge given 24 hours after the exercise bout. It is likely that the difference in results are in part due to the level of paralysis. Ditor et al. demonstrated that six 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, as they suggest that orthostatic tolerance is retained after exercise training.

Non-pharmacological Management Conclusions

Level 5 evidence exists, from two observational studies, to suggest that salt and fluid regulation, in combination with other pharmacological interventions, may reduce the symptoms of OH. However, these conclusions should be interpreted with caution, as no evidence exists on the effect of salt or fluid regulation alone in the management of OH in SCI patients. Currently, guidelines that suggest appropriate water and salt intake specific to individuals 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 physiological responses during sub-maximal, but not maximal, upper extremity exercises; but other studies have generated evidence that contradicts this. There is also Level 2 evidence from small, lower-quality RCTs – that FES is an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in individuals with SCI. Level 2 evidence exists that simultaneous upper extremity exercises may increase orthostatic tolerance during a progressive tilt exercise in individuals with paraplegia, but not tetraplegia; In addition, Level 4 evidence exists that 6 months of body-weight support treadmill training similarly does not substantially improve orthostatic tolerance during a tilt test.

Discussion

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

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

FES is one of the only non-pharmacological interventions which 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 if 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 non-pharmacological interventions for OH post-SCI, Gillis et al. stated that “FES of the legs holds the most promise” with an approximate 8/4 Hg reduction in BP fall during an orthostatic challenge.

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

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Table 1

Signs and Symptoms of Orthostatic Hypotension

Table 2

Factors Predisposing to OH following SCI

- Multi-factorial
- Loss of tonic sympathetic control,
- Altered baroreceptor sensitivity,
- Lack of skeletal muscle pumps, ,
- Cardiovascular de-conditioning,
- Altered salt and water balance

Table 3
Pharmacological Management and Fluid and Salt Intake for the Management of OH in SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Nieshoff et al. 2004; USA PEDro=5 RCT N=4	Population: 4 chronic, complete tetraplegia. Treatment: Midodrine 5mg, 10mg, or placebo. Double-blind, placebo-controlled cross-over design. OM: Cardiovascular measurement.	1 Midodrine, 10 mg elevated systolic blood pressure (BP) during exercise in 3 participants. Peak systolic BPs ranged from 90 to 126 mmHg under baseline and placebo conditions, 114–148 after 5 mg of midodrine, and 104 to 200 mmHg after 10 mg. 2 Two participants demonstrated ↓perceived exertion and ↑VO ₂ . 3 No adverse effects of midodrine.
Senard et al. 1991; France Downs & Black score=11 Pre-post N=7	Population: 45-year old male, chronic complete paraplegia; 6 non-SCI male controls. Treatment: Clonidine_(150µg, 2X/day) and midodrine_(specific alpha 1-agonist) (10mg, 2X daily). OM: BP, heart parameters, plasma catecholamine, alpha-adrenoceptor sensitivity.	1 The increase in systolic BP induced by midodrine (10 mg) was significantly higher in the patient (change of 56 mmHg) than in controls (change of 15 mmHg). 2 Midodrine and clonidine, either alone or in combination, led to increased resting BP and decreased severity of OH.
Barber et al. 2000; USA Downs & Black score=7 Case Series N=2	Population: 2 patients, acute complete motor tetraplegia. Treatment: fludrocortisone acetate 0.1mg 4X/day or midodrine 10mg 3X/day. OM: BP, HR, and symptoms of OH.	1 Fludrocortisone in both patients resulted in pitting oedema of hands and lower limbs. No effect of fludrocortisone on OH. 2 Initiation of the midodrine hydrochloride resolved orthostatic symptoms in both individuals without any complications.
Frisbie & Steele 1997; USA Downs & Black score=18 Observational N=231	Population: chronic SCI. Treatment: Retrospective chart review of ephedrine use (n=30), salt supplementation (n=6), fludrocortisone (n=3) or physical therapy. OM: OH symptoms, serum sodium, and urine osmolality.	1 4 patients on ephedrine commenced salt supplementation with meals. 2 Low blood sodium found in 54% of the OH patients and 16% of those without, p < 0.001.
Frisbie 2004; USA Downs & Black score=9 Observational N=4	Population: Complete cervical tetraplegia Treatment: Evaluation of urinary salt and water output in relation to prescribed dose of ephedrine (dose range from 0 to 100mg daily). OM: Severity of OH, urinary output.	1 A decreased dose of ephedrine (and OH severity), increased: mean daily output of urine sodium (from 50 to 181 mEq); creatinine secretion; water excretion; and sodium concentration; and a decrease in urine osmolality. 2 Estimated daily intake of salt and water was inversely related to the ephedrine requirement; greater salt and water intake may lead to more balanced renal action
Mukand et al. 2001; USA Downs & Black score=10 Case Report N=1	Population: 21-year old male; C6 tetraplegia. Treatment: Midodrine (2.5 to 15mg 3X/day). OM: BP and symptoms of OH.	1 Gradual increase of midodrine dose from 2.5mg to 10 mg (at 0800, 1200 and 1600 hrs) resulted in resolution of symptoms and orthostasis. Patient became able to participate fully in rehabilitation program.
Groomes et al. 1991; USA Downs & Black score=9 Case Report N=1	Population: 28-year-old, chronic C5 tetraplegia. Treatment: Ergotamine (2mg), daily combined with fludrocortisone (0.1 – 0.05mg). OM: BP.	1 Following 10 days with fludrocortisone, patient was able to tolerate sitting. Following additional ergotamine, the patient was able to tolerate an upright position without symptoms

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Muneta et al. 1992; Japan Downs & Black score=9 Case Report N=1	<p>Population: 72-year old SCI woman with paroxysmal hypotension.</p> <p>Treatment: Several weeks of salt supplement (7 then 15g/day), followed by L-threo-3,4-dihydroxyphenylserine (100mg to 600mg/day).</p> <p>OM: BP, serum catecholamines, plasma renin activity.</p>	<p>1 After salt supplement, an increase in BP and norepinephrine were observed after sitting; as was a decrease in basal plasma renin activity.</p> <p>2 Addition of L-threo-3,4-dihydroxyphenylserine for 2 weeks resulted in a 5 – 10 fold elevation in catecholamines without any apparent increase in resting BP.</p> <p>3 Significant improvement in the symptoms of paroxysmal hypotension; patient became able to participate in rehabilitation program.</p>

Table 4

Pressure Interventions for Management of OH in SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Hopman et al. 1998; USA PEDro=5 RCT N=9	Population: 9 SCI males; 5 tetraplegia, 4 paraplegia; 8 complete, 1 incomplete Treatment: Maximal arm ergometer tests while: 1) sitting; 2) supine; 3) sitting plus an anti-G suit; 4) sitting plus stockings, and an abdominal binder; and 5) sitting plus FES of the leg muscles. OM: Oxygen uptake, carbon dioxide output, respiratory parameters, HR, BP.	<ol style="list-style-type: none"> 1 Supine posture increased peak VO2 in tetraplegia, but reduced HR in paraplegia compared to sitting. 2 There was no effect of the anti-G suit, stockings plus abdominal binder, or FES on VO2, HR, 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. 1998; Netherlands PEDro=5 RCT N=9	Population: as above Treatment: as above, except sub-maximal exercise OM: as above	<ol style="list-style-type: none"> 1 Tetraplegia: increase VO2, cardiac output, stroke volume, BP and stroke volume with FES; increase cardiac output, and stroke volume and decrease HR with binders and stockings; decrease HR and increase BP with anti-G suit. 2 Paraplegia: increase VO2 and decrease HR with FES; decrease VO2 and HR with anti-G suit; decrease VO2 with stockings and binders.
Huang et al. 1983; USA PEDro = 5 RCT N=27	Population: 27, C4-C7, acute tetraplegia Treatment: Inflatable abdominal corset; bilateral pneumatic leg splints. OM: Respiratory rate, tidal volume, HR, systolic BP, diastolic BP.	<ol style="list-style-type: none"> 1 Assistive compressive devices do not improve pulmonary ventilatory parameters during postural changes 2 Assistive devices had no effect on systolic BP except in the 20° and 45° head-up positions (p<0.01). The 45° position, abdominal corset was significantly better than pneumatic leg splints at maintaining systolic BP. Same trend for diastolic BP. 3 Both devices failed to decrease HR in 20° head-down position; significant effect of assistive devices on increasing HR in the 20° and 45° head-up positions (p<0.01)
Krassioukov & Harkema 2006; Canada Downs & Black score=17 Prospective Controlled Trial N=20	Population: 6 complete tetraplegia, 5 complete paraplegia; 9 able-bodied controls. Treatment: With and without harness for locomotor training while supine, sitting and standing. OM: BP, HR.	<ol style="list-style-type: none"> 1 Orthostatic stress significantly decreased arterial BP only in individuals with cervical SCI (p < 0.05). 2 Harness application had no effect on cardiovascular parameters in able-bodied individuals. Diastolic BP was significantly increased in those with SCI 3 Orthostatic changes in cervical SCI when sitting were improved by harness application; no improvement while standing.
Kerk et al. 1995; USA Downs & Black score=13 Prospective Controlled Trial N=6	Population: Chronic, complete paraplegia. Treatment: Cross-over design: abdominal binder versus no abdominal binder. OM: BP, HR, VO2max, respiratory parameters, and wheelchair propulsion.	<ol style="list-style-type: none"> 1 Mean increase of 31 %, in 5 subjects, in forced vital capacity with binder; not statistically significant, but may be due to the sixth subject experiencing a 18% decrease in forced vital capacity when wearing the binder.
Vallbona et al. 1963; USA Downs & Black score = 13 Pre-post	Population: 12 chronic tetraplegia, 5 chronic paraplegia.	<ol style="list-style-type: none"> 1 Pressure suit attenuated the increase in HR (p>0.2; not significant) and drop in systolic and diastolic BPs (p<0.005; significant) during passive tilt in patients with tetraplegia.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
N=17	<p>Treatment: Pressure suit inflated to plus 30 cm of water.</p> <p>OM: Presence of symptoms, HR, systolic and diastolic BP.</p>	<p>2 In terms of HR and systolic BP, patients with paraplegia responded to passive tilting in a pressure suit similarly to passive tilting without the suit. However, an increase in diastolic BP was observed.</p>

HR: heart rate; BP: blood pressure; VO2max: maximum oxygen consumption

Table 5

FES on OH in SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Eliokda et al. 2000; USA PEDro=5 RCT N=5	Population: acute, complete, 2 tetraplegia 3 paraplegia. Treatment: Tilt table - 6 minutes at each tilt angle (15, 30, 45, 60 degrees). OM: HR, BP, perceived exertion.	<ol style="list-style-type: none"> 1 At all tilt angles, systolic BP was significantly lower when FNS was not applied, and differences were more marked with increasing tilt. 2 Progressive decrease in BP with increasing tilt angle, and thus a less pronounced FNS condition. 3 <i>Post hoc</i> analysis showed that HR was significantly higher with versus without FNS at 60 degrees tilt.
Faghri & Yount 2002; USA PEDro=5 RCT N=29	Population: 7 paraplegia, 7 tetraplegia; 4 incomplete, 10 complete, 15 controls. Treatment: Standing with or without FES; voluntary tiptoe contractions while standing for controls. OM: Hemodynamic parameters. while supine-sitting-30 min standing.	<ol style="list-style-type: none"> 1 BP reductions ($p < 0.05$) of up to 10% for SCI subjects sitting to passive standing; minimal changes when moving to FES standing. 2 After 30 min of passive standing (no FES), there was a reduction in stroke volume and cardiac output. 3 After 30 min of FES standing, pre-standing haemodynamics were maintained, except for a significant reduction in stroke volume.
Sampson et al. 2000; USA PEDro=5 RCT N=6	Population: Complete, 3 acute, 3 chronic (above T6). Treatment: With and without lower- extremity FES while tilted in 10° increments every 3 minutes, from 0–90° with varying intensities of stimulation. OM: BP, syncope score.	<ol style="list-style-type: none"> 1 Increase HR in both groups with increases in incline angle. 2 Mean diastolic BP was lower in subjects in acute versus chronic SCI stage. 3 Increase systolic and diastolic BP with increased stimulation intensities; decrease BP with increases in incline angle ($p < .001$) regardless of the site of stimulation. 4 Subjects tolerated higher angles of incline with higher FES intensities.
Faghri et al. 2001; USA Downs & Black score=22 Prospective Controlled Trial N= 14	Population: 7 tetraplegia, 7 paraplegia; 4 incomplete; 10 complete. Treatment: FES-augmented standing and non-FES standing, for 30min duration. OM: Hemodynamic parameters.	<ol style="list-style-type: none"> 1 BP changed 8–9% when moving from sitting to passive standing (no FES). The augmented FES condition prevented BP change when moving from sitting to standing.
Raymond et al. 2002; Australia Downs & Black score=16 Prospective Controlled Trial N=16	Population: 8 complete paraplegia, 8 controls. Treatment: Lower-body negative pressure (LBNP). Subjects were evaluated: (1) during supine rest, (2) supine with sub-maximal arm crank exercises (ACE), (3) ACE+LBNP, and (4) for SCI only, ACE+LBNP+ leg electrical stimulation (ES). OM: HR, stroke volume, cardiac output.	<ol style="list-style-type: none"> 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. 1999; Australia Downs & Black score = 10 Prospective Controlled Trial N = 16	Population: 8 chronic complete paraplegia; 8 controls. Treatment: Electrical-stimulation-induced leg muscle contractions (ES) during orthostatic challenge to examine the effects on venous pooling. OM: HR, SV, Q, SBP, DBP, MAP, limb volumes, VO ₂ .	<ol style="list-style-type: none"> 1 During orthostatic challenge, HR and VO₂ did not differ significantly with ES compared to without ES. 2 ES during orthostatic challenge augmented SV by 13 ml/beat compared to without ES; Q increased by 0.7 l/min. SBP, DBP, or MAP with ES did not change significantly.

Author Year; Country Research Design Total Sample Size	Methods	Outcome
Faghri et al. 1992; USA Downs & Black score=14 Pre-post N=13	Population: 6 paraplegia, 7 tetraplegia. Treatment: FES-leg cycle ergometer training, 3X/week, for 12 weeks. OM: VO ₂ , pulmonary ventilation (V _e), respiratory exchange ratio (RER), BP, HR, stroke volume (SV) and cardiac output.	<ol style="list-style-type: none"> 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.
Davis et al. 1990; USA Downs & Black score=16 Pre-post N=12	Population: 12 paraplegia. Treatment: Sub-maximal and maximal arm- crank exercise with or without FES. OM: Peak VO ₂ , VE, perceived exertion respiratory exchange ratio (RER), BP, HR, resting stroke volume (SV) and cardiac output (Q), total peripheral resistance.	<ol style="list-style-type: none"> 1 No significant differences between the FES and Control groups in terms of peak VO₂, maximal HR, VE, respiratory exchange ratio, or perceived exertion. 2 No differences in power output or VO₂ during peripheral FES application; higher stroke volume and Q during the FES- induced leg contractions. Neither rest nor exercise HR were significantly influenced by lower limb FES in the FES group. 3 HR, SV and Q were not significantly altered at rest or during hybrid exercise in controls; decrease in the peripheral and overall ratings of perceived exertion. 4 No changes in BP, myocardial contractility, or ratings of perceived exertion during hybrid exercise versus non-FES conditions.
Chao & Cheing 2005; China Downs & Black score=15 Post N=16	Population: Complete motor tetraplegia. Treatment: Progressive head-up tilting manoeuvre with and without FES applied to 4 muscle groups. OM: BP, HR, perceived pre-syncope score.	<ol style="list-style-type: none"> 1 With increasing tilt angle, decrease in systolic and diastolic BP and increase in heart rate, with and without FES. 2 Adding FES to tilting significantly attenuated the drop in systolic and diastolic BP. Heart rate increased by 1.0±0.5 beats/min (p = .039) for every 15-degree increment in the tilt angle. 3 FES increased the overall mean standing time.

HR: heart rate; BP: blood pressure; VO₂: oxygen consumption

Exercise for OH in SCI

Table 6

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Lopes et al. 1984; USA PEDro=2 RCT N=12	Population: 5 tetraplegia, 1 paraplegia; 6 controls. Treatment: Random assignment to active exercise versus no upper limb exercises during tilt from 0-70 degrees by 10-degree increments at five-minute intervals until blood pressure dropped below 70/40. OM: BP, symptoms of hypotension.	1 No significant difference between the active upper extremity exercise group versus the non-exercise group with respect to tolerance to progressive vertical tilt.
Engelke et al. 1994; USA Downs & Black score=10 Prospective Controlled Trial N=10	Population: 10 paraplegia. Treatment: Maximal arm-crank exercise. Outcome Measures: BP, HR, forearm vascular resistance (FVR) and vasoactive hormone responses before and during 15 min of 70° head-up tilt (HUT).	1 HR increased similarly in the control and post-exercise conditions. 2 Reduction in systolic BP was significantly larger during HUT before than after arm-crank exercises 3 Post-exercise increase in FVR from supine to HUT was significantly greater in treatment 4 Carotid-cardiac baroreflex increased significantly after exercise 5 No difference in vasoactive hormone responses 6 No difference in either leg compliance or plasma volume
Ditor et al. 2005; Canada Downs & Black score=18 Pre-post N=8	Population: Sensory incomplete cervical SCI (C4-C5). Treatment: 6 months of body weight- supported treadmill training (BWSTT). Outcomes measures: HR, BP, and orthostatic responses, heart-rate variability.	1 Decrease in resting HR; no change in BP 2 No effect on BP or HR during the 60° Head Up Test. 3 A trend towards a relative exaggeration of the pressor response to orthostatic stress during the tilt test suggesting improved orthostatic tolerance.

HR: heart rate; BP: blood pressure