Autonomic Dysreflexia Following Spinal Cord Injury

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Key Points

The identification and removal of the possible trigger and subsequent decrease of afferent stimulation to the spinal cord is the most effective prevention strategy in clinical practice.

Botulinum toxin injections into the detrusor muscle or external urethral sphincter seem to be a safe and valuable therapeutic option in SCI patients who perform clean intermittent self-catheterization and have incontinence resistant to anticholinergic medications. Its use in the prevention of AD is less well defined.

Capsaicin and its analogue, resiniferatoxin, are effective in the management of AD in patients with SCI.

Anticholinergics do not appear to be sufficient for the management of AD in SCI.

Sacral deafferentation may reduce AD during urodynamic investigations.

Urinary bladder surgical augmentations may diminish or resolve episodes of AD.

Lidocaine anal block can limit the AD response in susceptible patients undergoing anorectal procedures.

Topical lidocaine may prevent AD during digital bowel stimulation but does not prevent AD during anorectal procedures.

Adequate anesthesia (spinal or epidural if possible) is needed with vaginal delivery, Caesarean delivery or instrumental delivery.

Anesthesiologists and surgeons dealing with SCI patients must know how to recognize the AD syndrome, how to prevent its occurrence and how to manage it.

Epidural anesthesia is preferred and effective for most women with AD during labour and delivery.

Anesthesia should be used during surgical procedures in individuals with SCI despite apparent lack of sensation.

Topical anesthetic is not effective for the prevention of AD during FES.

Nifedipine may be useful to prevent or control AD in SCI individuals; however, serious adverse effects from its use may occur similar to those reported in other populations.

Nitrates are commonly used in the control of AD in SCI; however, no studies have been done to show their effectiveness or safety in SCI.

Preliminary evidence suggests that captopril is effective for the management of AD in SCI.

There is limited evidence for the use of Terazosin as an agent for control of AD in SCI individuals.

Prazosin can prophylactically reduce severity and duration of AD episodes in SCI.

It is not known whether Phenoxybenzamine is effective for the management of AD in SCI.

Prostaglandin E2 is effective for reducing BP responses during eletroejaculation.

Sildenafil has no effect on AD responses in men with SCI during ejaculation.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin I-converting enzyme</td>
</tr>
<tr>
<td>AD</td>
<td>autonomic dysreflexia</td>
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<tr>
<td>AIS</td>
<td>ASIA Impairment Scale</td>
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<tr>
<td>AUA</td>
<td>American Urological Association</td>
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<tr>
<td>BND</td>
<td>bladder neck disorder</td>
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<tr>
<td>BoNT-A</td>
<td>botulinum toxin A</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
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<tr>
<td>DESD</td>
<td>detrusor external sphincter dyssynergia</td>
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<tr>
<td>DVT</td>
<td>deep vein thrombus</td>
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<td>ECG</td>
<td>electrocardiogram</td>
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<td>FES</td>
<td>functional electrical stimulation</td>
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<td>HR</td>
<td>heart rate</td>
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<td>IEMG</td>
<td>integrated electromyography</td>
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<td>IIQ-7</td>
<td>Incontinence Impact Questionnaire</td>
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<td>IU</td>
<td>international unit (measurement unit of drugs)</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
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<tr>
<td>M/F</td>
<td>male/female</td>
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<tr>
<td>NBD</td>
<td>neurogenic bowel disorder</td>
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<tr>
<td>Para</td>
<td>paraplegic</td>
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<tr>
<td>PDE5</td>
<td>phosphodiesterase type 5</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RTX</td>
<td>resiniferatoxin</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>SCI</td>
<td>spinal cord injury</td>
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<tr>
<td>Tetra</td>
<td>tetraplegic</td>
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<tr>
<td>TURS</td>
<td>transurethral sphincterotomy</td>
</tr>
<tr>
<td>UDI-6</td>
<td>Urogenital Distress Inventory</td>
</tr>
<tr>
<td>UUT</td>
<td>upper urinary tract</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
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</table>
Autonomic Dysreflexia
Following Spinal Cord Injury

1.0 Introduction

Autonomic dysreflexia (AD) is a clinical emergency in individuals with spinal cord injury (SCI). It commonly occurs in individuals with injury at level T6 and above (Mathias & Frankel 1988; Karlsson 1999; Teasell et al. 2000; Mathias & Frankel 2002). An episode of AD is usually characterized by acute elevation of arterial blood pressure (BP) and bradycardia (slow heart rate), which, on occasion, may be replaced by tachycardia (rapid heart rate). Objectively, an increase in systolic BP greater than 20–30mmHg is considered a dysreflexic episode (Teasell et al. 2000). Individuals with cervical and high thoracic SCI have resting arterial BPs that are approximately 15 to 20 mmHg lower than able-bodied individuals (Mathias & Bannister 2002; Claydon et al. 2006). As such, acute elevation of BP to normal or slightly elevated ranges could indicate AD in this population. Intensity of AD can vary from asymptomatic (Linsenmeyer et al. 1996), mild discomfort and headache to a life threatening emergency when systolic blood pressure can reach 300mmHg (Mathias & Frankel 2002) and symptoms can be severe. Untreated episodes of autonomic dysreflexia may have serious consequences, including intracranial hemorrhage, cardiac complications, retinal detachments, seizures and death (Yarkony et al. 1986; Pine et al. 1991; Eltorai et al. 1992; Valles et al. 2005). During an episode of AD, a significant increase in visceral sympathetic activity with coronary artery constriction can result in myocardial ischemia, even in the absence of coronary artery disease (Ho & Krassioukov 2010).

It has been observed that the higher the level of the SCI, the greater the degree of clinical manifestations of cardiovascular dysfunctions (Mathias & Frankel 1992; Curt et al. 1997; Krassioukov et al. 2003). Another crucial factor affecting the severity of AD is the degree of completeness of spinal injury as only 27% of incomplete tetraplegics presented with signs of AD compared to 91% of tetraplegics with complete lesions (Curt et al. 1997). AD is three times more prevalent in tetraplegics with a complete injury, in comparison to those with an incomplete injury (Curt et al. 1997). It is important to note, however, that although autonomic dysreflexia occurs more often in the chronic stage of spinal cord injury at or above the 6th thoracic segment, there is clinical evidence of early episodes of autonomic dysreflexia within the first days and weeks after the injury (Silver 2000; Krassioukov et al. 2003).

2.0 Pathophysiology of AD

AD is most commonly triggered by urinary bladder or colon irritation. However, many other causes have been reported in the literature (Teasell et al. 2000; Mathias & Frankel 2002). AD is caused by massive sympathetic discharge triggered by either noxious or non-noxious stimuli below the level of the SCI (Krassioukov & Claydon, 2006). Numerous reports of AD have been described in the literature: episodes are usually short-lived either due to treatment or inherently self-limiting. However, there are reports of AD triggered by a specific stimulus, which then continued to be present for a period of days to weeks (Elliott & Krassioukov 2006).

Numerous mechanisms have been proposed for the development of AD. It is known from animal studies that autonomic instability following SCI results from plastic changes occurring within the spinal and peripheral autonomic circuits in both the acute and chronic stages following injury (Mathias & Frankel 1988; Teasell et al. 2000; Mathias & Frankel 2002; Krassioukov 2006). The destruction of the descending vasomotor pathways results in the loss of inhibitory and excitatory supraspinal input to the sympathetic preganglionic neurons; this is currently considered the major contributor to unstable blood pressure control following SCI (Furlan et al. 2003). Furthermore, there is significant animal and human evidence suggesting that plastic changes within the spinal cord (specifically spinal sympathetic neurons and primary afferents) underlies the abnormal cardiovascular control and the development of AD following SCI. Altered sensitivity of peripheral alpha-adrenergic receptors (receptors in the
sympathetic nervous system) is one mechanism that may contribute to AD (Osborn et al. 1990; Arnold et al. 1995; Krassioukov & Weaver 1995, 1996; Karlsson 1999; Krassioukov et al. 1999; Krassioukov et al. 2002).

**Table 1: Signs and Symptoms**

- Severe bilateral pounding headache
- Feeling of anxiety/impending doom
- Profuse sweating above the level of injury
- Flushing and piloerection (body hair ‘stands on end’) above the level of injury
- Dry and pale skin due to vasoconstriction below the level of injury
- Blurred vision
- Nasal congestion
- Cardiac arrhythmias, atrial fibrillation

**3.0 Systematic Review on AD**

As knowledge is growing in the field of AD management in the SCI population, it is important to regularly review the literature and ensure that the information used both in research and practice is current and evidence-based. The aim of this section is to provide an overview of the current systematic reviews available in this area related to AD management in the SCI population.

**Table 2: Systematic Review on AD**

<table>
<thead>
<tr>
<th>Authors; Country</th>
<th>Date included in the review</th>
<th>Total Sample Size</th>
<th>Level of Evidence</th>
<th>Type of Study</th>
<th>Score</th>
<th>Methods</th>
<th>Databases</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krassioukov et al. 2009; Canada</td>
<td>Reviewed published articles from 1950 to 2007</td>
<td>N=31</td>
<td>PEDro scale – RCTs, Modified Downs and Black – non-RCTs</td>
<td>6 RCTs 11 pre-post 5 observational 5 case series 3 prospective controlled 1 case report</td>
<td>AMSTAR: 5</td>
<td>Literature search for English articles, practice guidelines, and review articles evaluating the efficacy of interventions related to autonomic dysreflexia (AD) in the spinal cord injury population. Interventions included non-pharmacologic and pharmacologic (nifedipine, captopril, terazosin, prazosin, phenoxybenzamine, prostaglandin E2, sildenafil, and nitrates) management of AD, as well as preventative strategies to reduce episodes and symptoms of AD from common triggers.</td>
<td>PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO</td>
<td>1. There is strong evidence (level 1 and 2) supporting the use of intravesical resiniferatoxin as well as intersphincteric anal block with lidocaine for the management of AD in SCI patients. 2. There is also evidence that topical lidocaine does not limit or prevent AD in susceptible patients during anorectal procedures and that there is no beneficial effect of topical anesthetic in the prevention of AD during FES. 3. Nifedipine is the only pharmacological agent supported by controlled trials (Level 2) in the prevention of dangerous blood pressure reactions. 4. There is low-level evidence (level 4 and 5) for the effectiveness of botulinum toxin injections into the detrusor muscle and use of intravesical capsaicin and anticholinergics in limiting AD. 5. There is conflicting level 4 evidence regarding the effectiveness of sacral deafferentation in the prevention of AD 6. There is level 5 evidence (clinical consensus) but there are no clinical studies that support the use of nitrates in the acute management of AD. 7. There is conflicting evidence with the use of phenoxybenzamine for AD management. There is level 2 evidence that sildenafil citrate has no effect on blood pressure changes during AD episodes induced by vibrostimulation in men with SCI.</td>
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<tr>
<td>Authors; Country Date included in the review Total Sample Size Level of Evidence Type of Study Score</td>
<td>Methods Databases</td>
<td>Conclusions</td>
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<td>Courtois et al. 2012 Canada</td>
<td>Methods: Literature search for English or French language articles of all levels of evidence that provided scientific evidence on the specific treatment of AD following SCI in human males. The review focused on treatments that could be implemented at home during sexual activities therefore studies on intravenous treatment were generally rejected (with the exception of one). Also excluded were studies that only mentioned a procedural management of AD in their methods without giving specific results. Interventions included non-pharmacologic and pharmacologic (nifedipine, prazosin, prostaglandin E2, sildenafil, captopril, terazosin, doxazosin, phenoxymethylamine) management of AD, as well as preventative strategies to reduce episodes and symptoms of AD from common triggers Outcome measure: seated blood pressure (SBP), incidence of AD.</td>
<td>1. 37 papers on the specific treatment of AD showed that nifedipine, prazosin, captopril and clonidine are candidates in the context of sexual activities. 2. Prazosin, has an initial hypotensive effect requiring to begin treatment 12h before intercourse, which makes it less ideal for spontaneous sexual activities. 3. Captopril has an initial hypotensive effect and was only studied in acute AD. Its usefulness in prophylaxis remains to be demonstrated. 4. Clonidine has successfully been used clinically for decades, but never studied in randomized control trials. 5. Nifedipine remains the most widely studied and significant treatment of AD whether in acute or prophylactic conditions. Recent concerns suggest increased cardiovascular risks with sublingual nifedipine in non-SCI populations, but negative long-term effects have not been reported in the SCI population.</td>
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<tr>
<td>Reviewed published articles from 1948 to 2011 N=37</td>
<td>Databases: PubMed/MEDLINE</td>
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<tr>
<td>Level of Evidence: Methodological quality not assessed</td>
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<td>Types of studies: Information not provided</td>
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<td>AMSTAR: 2</td>
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**Discussion**

We found two systematic reviews looking at the effectiveness of AD management interventions.

Courtois et al. (2012) reported that 37 papers on the specific treatment of AD showed that nifedipine, prazosin, captopril and clonidine are candidates in the context of sexual activity. Krassioukov et al. (2009) found strong evidence that intravesical resiniferatoxin and intersphincteric anal block with lidocaine were effective in the prevention of AD episodes. The same authors also found evidence that nifedipine is useful in the prevention of dangerous blood pressure elevation during diagnostic or therapeutic procedures. Krassioukov et al. (2009) also found that topical lidocaine is not beneficial for the management of AD in SCI population. Finally, these authors found only limited evidence supporting the use of botulinum toxin injections into the detrusor muscle and no support for the use of anticholinergics for AD management. Although the authors found that higher quality research assessing the management of AD in the SCI population is needed, they concluded that careful evaluation of individuals with SCI and increased awareness and early recognition of possible triggers that could result in AD remains the most effective approach in AD management.

**4.0 Management**

There is a well-established protocol for the management of AD developed by the Consortium for Spinal Cord Medicine (Consortium for Spinal Cord Medicine 1997). In patients with spinal cord injury, appropriate bladder and bowel routines, in addition to pressure sore prevention are the most effective measures for the prevention of autonomic dysreflexia. However, for each individual, the identification
and elimination of specific triggers for autonomic dysreflexia should also be employed to manage and prevent episodes of autonomic dysreflexia (Teasell et al. 2000; Mathias & Frankel 2002; Blackmer 2003).

There is growing evidence that education on knowledge and management of this life-threatening condition is crucial for both medical personnel and individuals with SCI (McGillivray et al. 2009).

When AD develops, the initial management of an episode involves placing the patient in an upright position to take advantage of an orthostatic reduction in blood pressure, and the loosening of any tight clothing (Consortium for Spinal Cord Medicine 1997). Throughout the episode, the blood pressure should be checked at 5 minute intervals. It is then necessary to search for and eliminate the precipitating stimulus where one can be identified, most commonly (in 85% of cases) related to either bladder distension or bowel impaction (Teasell et al. 2000; Mathias & Frankel 2002). The use of antihypertensive drugs should be considered as a last resort, but may be necessary if the systolic blood pressure remains at 150 mmHg or greater following the steps outlined above (Consortium for Spinal Cord Medicine 1997). The goal of such an intervention is to alleviate symptoms and avoid the complications associated with uncontrolled hypertension (Yarkony et al. 1986; Pine et al. 1991; Eltorai et al. 1992; Valles et al. 2005).

5.0 Prevention Strategies

The most effective approach to AD is the prevention of occurrence of this disabling and life threatening condition (Braddom & Rocco 1991). This includes careful evaluation of individuals with SCI and early recognition of possible triggers that could result in AD. Improved clinician awareness of AD and greater attention to the need to eliminate noxious stimuli in individuals with SCI is a priority. Clinicians, family members, and caregivers should be aware that increased afferent stimulation (e.g., via surgery, invasive investigational procedures, labour and birth) to persons with SCI will increase the risk for development of AD. A variety of procedures can be used to prevent episodes of AD.

5.1 Prevention of AD during Bladder Procedures

Urinary bladder irritation or stimulation is the major trigger of AD following SCI (McGuire & Kumar, 1986; Linsenmeyer et al. 1996; Giannantoni et al. 1998; Teasell et al. 2000; Mathias & Frankel 2002). A bladder management program and continuous urological follow-up are important elements of the medical care of individuals with SCI (Waites et al. 1993a; Vaidyanathan et al. 1994; Vaidyanathan et al. 2004). An established bladder management program with intermittent catheterization or an indwelling Foley catheter allows individuals with SCI to plan for bladder emptying when convenient or necessary (Consortium for Spinal Cord Medicine 2006). However, there are no studies that specifically assess the effect of bladder management programs on the rate of occurrence of autonomic dysreflexia.

During the last decade, urological follow-up including annual urodynamic evaluations and cystoscopy (depending on the bladder management program), have decreased the frequency of urinary tract infections and the development of renal failure in individuals with SCI (Waites et al. 1993a; Waites et al. 1993b; DeVivo et al. 1999). However, conservative management is not always successful and alternative strategies (e.g. application of Botulinum toxin, capsaicin, anticholinergics, sacral denervation and bladder and urethral sphincter surgery) are sometimes needed to decrease afferent stimulation from the urinary bladder to prevent development of AD. In addition, urodynamic procedures and cystoscopy are associated with significant activation of urinary bladder afferents and have the potential to trigger AD (Linsenmeyer et al. 1996; Dykstra et al. 1987; Snow et al. 1978;
Chancellor et al. 1993) and therefore also require strategies to reduce afferent stimulation during those procedures.

5.1.1 Botulinum Toxin

Injection of Botulinum toxin into the detrusor muscle is a treatment for urinary incontinence secondary to neurogenic detrusor overactivity while injection into the external urethral sphincter is a treatment for detrusor-sphincter dyssynergia and high post void residual urines.

Table 3: Botulinum Toxin and AD

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Research Design</th>
<th>Sample Size</th>
<th>Population</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen &amp; Kuo 2012; Taiwan</td>
<td>Pre-post</td>
<td>N=49 (with AD=34)</td>
<td>49 patients (31M, 18F) with SCI and detrusor sphincter dyssynergia; Level of SCI: 27 cervical, 22 thoracic; mean age in yrs: 41.6, range 22-74; mean DOI in yrs: 8, range 1-35.</td>
<td>Treatment: Patients received two sets of 200 U BoNT-A injections into the detrusor at baseline and 6 months later.</td>
<td>1. 15 patients did not have AD at baseline or after treatment.</td>
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<td>Outcome Measures: Improvement in the severity of AD; net change in the grade of incontinence; net changes in the scores of the Urogenital Distress Inventory (UDI-6); Incontinence Impact Questionnaire; quality of life index; urodynamic parameters.</td>
<td>2. AD was completely resolved in 3 patients, and improved in 18; treatment made no difference in 3 patients and AD was exacerbated in 10.</td>
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<td>3. No significant differences in any urodynamic variables between patients with and without AD.</td>
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<td>4. A significantly greater improvement in the UDI-6 was noted in patients without AD and those in whom AD improved than in those with AD. Occurrence of AD was not significantly associated with persistent urinary incontinence after the BoNT-A injections.</td>
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<td>5. No significant difference in the quality of life index between patients with and without AD at the end point.</td>
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</table>

| Chen et al. 2008; Taiwan | Pre-post | N=20 (with AD=4) | 20 suprasacral SCI subjects with detrusor external sphincter dyssynergia (DESD); Mean age 37.9 (15.7); 17 male; 12 cervical, 3 thoracic, 5 lumbar; AIS diagnosis: 11 AIS-A, 2 AIS-B, 4 AIS-C, 3 AIS-D. | Treatment: A single dose of 100 IU botulinum toxin A was applied into the external urethral sphincter via cystoscopy. | 1. 4 patients who had AD symptoms before treatment reported decreased frequency and intensity of AD. |
| | | | | Outcome Measures: maximal detrusor pressure, maximal urethral pressure, maximal detrusor leak point pressure, integrated electromyography (IEMG) of the external urethral sphincter and, maximal pressure on static urethral pressure profilometry, recorded before and 4 weeks after the injection; post-voiding residues, measured 1, 2, 3, and 6 months post-injection. | 2. There was significant reduction in the IEMG (from 16.7(13.6) to 12.5(12.9) μV), as well as static urethral pressure (from 139.4(40.5) to 104.8(30.5) cmH₂O) and maximal urethral pressure (from 107.5(69.1) to 80.2(35.7) cmH₂O). |
| | | | | | 3. There was no significant difference in the maximal detrusor pressure or detrusor leak point pressure. |
| | | | | | 4. Post-voiding residues were significantly reduced at 1st, 2nd, 3rd, and 6th months post-injection. |

<p>| Kuo 2008; Taiwan | Pre-post | N=33 (with AD=6) | 33 subjects suffering from detrusor sphincter dyssynergia and urinary incontinence (including 9 individuals with cervical SCI, 12 with thoracic SCI, 5 with lumbar SCI, 5 multiple sclerosis and 2 transverse myelitis patients); age range 23-71. | Treatment: transurethral sphincter botox injections, injecting 100 units of botox in 4 ml | 1. 3/6 patients experienced decreased symptoms of AD post-treatment. |
| | | | | | 2. Urodynamic parameters showed significant improvement in voiding detrusor pressure (45.7(22.7) vs. 30.7(15.5) cmH₂O), maximum flow rate (6.8(5.7) vs. 9.2(7.7) ml/sec) and post-void residual volume (160(124) vs. 75(105) ml). |</p>
<table>
<thead>
<tr>
<th>Author Year; Country Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schurch et al. 2000; Switzerland Pre-post N initial=31 N final=19</td>
<td>normal saline into eight sites of the urethral sphincter. <strong>Outcome Measures</strong>: video-urodynamic studies; Urogenital Distress Inventory short form (UDI-6); Incontinence Impact Questionnaire (IIQ-7) short form.</td>
<td>3. IIQ-7 scores were significantly improved, but not the UDI-6 scores.</td>
</tr>
<tr>
<td>Dykstra et al. 1988; USA Pre-post N=11 (with AD=7)</td>
<td><strong>Population</strong>: Mean age: 36.7 yrs, mean DOI=60.2 months; 18 subjects with paraplegia, 3 with tetraplegia, 17 subjects with complete injuries, 4 with incomplete injuries, incontinence resistant to anticholinergic medication. <strong>Treatment</strong>: Botulinum-A toxin was injected (200-300 units) into the detrusor muscle. <strong>Outcome Measures</strong>: voiding and detrusor pressure, diary of incontinence, AD symptoms at 6, 16, and 36-wks.</td>
<td>1. At 6-week follow-up 17/19 patients were completely continent. 2. 3 patients with tetraplegia with severe AD with bladder emptying found this disappeared after treatment. 1. Urethral pressure profile decreased 27 cm H2O (n=7). 2. Self-assessed improvement of AD symptoms in 5 of 7 AD patients. 3. Toxin effects lasted an average of 50 days.</td>
</tr>
</tbody>
</table>

**Discussion**

Five pre-post studies (n=132) (Dykstra et al. 1988; Schurch et al. 2000; Chen et al. 2008; Kuo 2008; Chen & Kuo 2012) found injection of Botulinum toxin into the detrusor muscle or bladder sphincter to be an effective method for treating urinary incontinence or retention secondary to neurogenic detrusor overactivity and bladder sphincter dyssynergia. In these conditions, injections of the Botulinum toxin either allowed increased urinary bladder capacity (i.e., reduced overactivity of the bladder) or facilitated improved evacuation of urine (reduced bladder sphincter dyssynergia). The duration of effect was reported to last up to 9 months (Schurch et al. 2000). All studies were level 4 and showed positive effects. In fact, following treatment with Botulinum toxin, 3 individuals reported fewer episodes of AD (Kuo 2008), 4 individuals reported decreased frequency and intensity of AD (Chen et al. 2008), 3 individuals who experienced severe AD during bladder emptying reported disappearance of these symptoms altogether (Schurch et al. 2000), 3 individuals reported AD was completely resolved (Chen & Kuo 2012), and 18 individuals experienced improvement in AD symptoms (Chen & Kuo 2012). While the evidence suggests that Botulinum toxin may be a viable treatment for neurogenic detrusor overactivity, the evidence supporting the application of Botulinum toxin specifically for the prevention of AD is inconclusive.

**Conclusion**

*There is level 4 evidence (from 5 pre-post studies) (Dykstra et al. 1988; Schurch et al. 2000; Chen et al. 2008; Kuo 2008; Chen & Kuo 2012) that Botulinum toxin injections into the detrusor muscle or external urethral sphincter seem to be a safe and valuable therapeutic option in SCI patients who perform clean intermittent self-catheterization and have incontinence resistant to anticholinergic medications.*
5.1.2 Intravesical Capsaicin

Capsaicin is an extract from red pepper and exerts a selective action on certain sensory nerves, most notably those involved in reflex contractions of the bladder after spinal cord injury.

Table 4: Capsaicin

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Score Research Design</th>
<th>Sample Size</th>
<th>Population</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. 2003; USA</td>
<td>PEDro=9 RCT</td>
<td>N=36</td>
<td>22 males, 14 females, neurologically impaired patients (20 SCI, 7 multiple sclerosis, 9 other) with urodynamically verified detrusor hyperreflexia.</td>
<td>1. No statistical significance due to small sample sizes. 2. Intravesical RTX administration was well tolerated. This patient group was refractory to all previous oral pharmacologic therapy, yet some patients responded with improvement in bladder capacity and continence function shortly after RTX administration. 3. In some cases, mean cystometric capacity increased up to 500% over baseline. 4. Incontinence episodes decreased by over 50% for the 2 highest doses. 5. No data available on long term effect of RXT on AD.</td>
<td></td>
</tr>
<tr>
<td>Giannantoni et al. 2002; Italy</td>
<td>PEDro=6 RCT</td>
<td>N=23</td>
<td>Refractory detrusor hyperreflexia. Treatment: Randomized two treatments a) single dose of 2 mM. capsaicin in 30 ml ethanol plus 70 ml 0.9% sodium chloride OR b) 100 mM. resiniferatoxin in 100 ml 0.9% sodium chloride.</td>
<td>1. Capsaicin group showed no significant urodynamic or clinical improvements at 30 and 60 days. 2. Resiniferatoxin group demonstrated significant urodynamic improvement at 30 and 60 days. 3. Most patients receiving capsaicin, but none receiving resiniferatoxin developed AD, limb spasms, suprapubic discomfort and hematuria.</td>
<td></td>
</tr>
<tr>
<td>Igawa et al. 2003; Japan</td>
<td>Pre-post</td>
<td>N=7</td>
<td>5 subjects with cervical injuries and 2 subjects with thoracic injuries. Treatment: bladder instillation with capsaicin solution under general anesthesia.</td>
<td>1. Capsaicin attenuated elevated BP secondary to bladder distention (empty or full) post-treatment. 2. In all individuals, episodes of AD become negligible and well tolerated &gt; 3 months.</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

One RCT (n=23) (Giannantoni et al. 2002) and one pre-post study (n=7) (Igawa et al. 2003) evaluated the effect of capsaicin. Capsaicin exerts a selective action on those sensory nerves involved in reflex contractions of the bladder.
contractions of the bladder after SCI. In their pre-post study, Igawa et al. demonstrated that intravesical capsaicin decreased episodes of AD in patients with SCI during catheterization, thereby suggesting the therapeutic potential of intravesical capsaicin for both AD and detrusor hyperreflexia in SCI patients (Igawa et al. 2003). Giannantoni et al. in a high quality RCT (PEDro=6) used an analogue of capsaicin (resiniferatoxin RXT) that is more than 1,000 times more potent in desensitizing C-fiber bladder afferents and found reduced episodes of AD (Giannantoni et al. 2002). In addition, investigators found that intravesical administration of resiniferatoxin was superior to that of intravesical capsaicin in terms of urodynamic results and clinical benefits in SCI patients within 60 days of treatment and did not cause the inflammatory side effects associated with capsaicin. Long-term effects of capsaicin or resiniferatoxin on AD, however, have not been evaluated.

Conclusion

There is level 4 evidence (from 1 pre-post study) (Igawa et el. 2003) that intravesical capsaicin is effective for reducing episodes of AD in SCI.

There is level 1 evidence (from 2 RCTs) (Kim et al. 2003; Giannantoni et al. 2002) that intravesical resiniferatoxin is effective for reducing episodes of AD in patients with SCI.

There is level 1 evidence (from 1 RCT) (Giannantoni et al. 2002) that intravesical resiniferatoxin is more effective than intravesical capsaicin.

| Capsaicin and its analogue, resiniferatoxin, are effective in reducing the episodes of AD in patients with SCI. |

5.1.3 Anticholinergics

Anticholinergics are a class of medications that inhibit the binding of the neurotransmitter acetylcholine to its receptors. Acetylcholine is released by the parasympathetic nerve fibers innervating the urinary bladder and contributes to detrusor contraction and activation of the bladder afferents. These afferent stimuli activate spinal sympathetic circuits that trigger AD. In theory, anticholinergic agents could therefore decrease afferent activation, and consequently AD.

Table 5: Anticholinergics

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giannantoni et al. 1998; Italy Observational N=48</td>
<td>Population: SCI patients. Treatment: anticholinergic drugs. Outcome Measures: neurological and urological examination and urodynamic evaluation with concurrent recording of blood pressure, heart rate, symptoms of AD.</td>
<td>1. Presence of detrusor uninhibited contractions and bladder distension both contribute to AD crisis. 2. Treatment with anticholinergic drugs is not sufficient to prevent AD starting from the bladder, unless it induces detrusor areflexia.</td>
<td></td>
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</tbody>
</table>

Discussion

Only one study, employing an observational cross-sectional design (n=48), has examined the use of anticholinergics (Giannantoni et al. 1998). These authors did not observe a correlation between anticholinergic drugs and reduced incidence of AD, unless treatment resulted in detrusor areflexia.
Conclusion

There is level 5 evidence that anticholinergics (from 1 observational study) (Giannantoni et al. 1998) are not associated with reduced incidence of AD episodes.

Anticholinergics do not appear to be sufficient for the management of AD in SCI.

5.1.4 Sacral Denervation

When detrusor hyperreflexia post SCI does not respond to conservative treatment, and patients are not eligible for ventral sacral root stimulation for electrically induced micturition, sacral bladder denervation may be considered as a stand-alone procedure to treat urinary incontinence and AD.

Table 6: Sacral Denervation

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kutzenberger 2007; Germany Case series</td>
<td>Population: 440 (190 tetra, 274 para) SCI patients ranging from 0.5 to 46 years since injury. Treatment: Sacral deafferentation and implantation of a sacral anterior root stimulator. Outcome Measures: Presence of AD.</td>
<td>1. Autonomic dysreflexia disappeared in all cases with the exception of two. In these individuals, blood pressure was maintained at less dangerous levels.</td>
</tr>
<tr>
<td>Hohenfellner et al. 2001; Germany Pre-post N=9 (with AD=5)</td>
<td>Population: detrusor hyperreflexia. Treatment: sacral bladder denervation. Outcome Measures: bladder capacity, blood pressure, symptomatic AD.</td>
<td>1. Episodes of detrusor hyperreflexia and AD were eliminated in all cases. 2. In the 5 patients with AD, both SBP and DBP were reduced 196(16.9) to 124(9.3) mmHg and 114(5.1) to 76(5.1) mmHg, respectively.</td>
</tr>
<tr>
<td>Schurch et al. 1998; Switzerland Case series N=10</td>
<td>Population: 10 SCI patients with AD. Treatment: sacral deafferentation. Outcome measures: continuous non-invasive recordings of BP and HR during urodynamic recordings, pre- and post-operative data.</td>
<td>1. There was a marked elevation in systolic and diastolic BP with bradycardia during the urodynamic examination in all eight patients, despite complete intra-operative deafferentation of the bladder in five. 3. AD persisted in patients with SCI even post complete sacral deafferentation, consistently occurring during the stimulation-induced voiding phase.</td>
</tr>
</tbody>
</table>

Discussion

Three level 4 studies (aggregate n=459) (Schurch et al. 1998; Hohenfellner et al. 2001; Kutzenberger 2007) examining sacral denervation have reported conflicting results in response to this procedure. Hohenfellner et al. reported that sacral bladder denervation is a valuable treatment option for eliminating detrusor hyperreflexia and AD in all 9 of their subjects (Hohenfellner et al. 2001). However, in Schurch et al.’s 10 subjects, it was shown that complete bladder deafferentation does not abolish AD during bladder urodynamic investigations. In a review of 440 patients, Kutzenberger saw sacral deafferentation eliminate AD in 438 of them.

Conclusion

There is level 4 evidence (from one pre-post study and one case series study) (Hohenfellner et al. 2001; Kutzenberger 2007) that sacral deafferentation may be effective in preventing AD.
5.1.5 Bladder and Urethral Sphincter Surgery

The association between episodes of AD and the presence of detrusor sphincter dyssynergia, high intravesical pressure and urethral pressure has led to the development of surgical procedures to alleviate voiding dysfunctions and consequently AD.

**Table 7: Bladder and Urethral Sphincter Surgery**

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Score Research Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Merwe et al. 2012; South Africa</td>
<td>Case series</td>
<td>N=28</td>
<td>Population: 28 male patients with neuropathic bladder dysfunction after SCI who had dual flange Memokath stents inserted in the period March 2008 to October 2011; Age in yrs: mean 37.4, range 23-64; Level of injury: 23 cervical, 5 thoracic. Treatment: Stents were placed rather than performing an external sphincterotomy in selected patients. With the patient under deep general anesthesia, a thermosensitive expandable metallic stent was positioned over the internal and external urethral sphincters; patients were followed-up at 1 month and again between 3 and 6 months. Outcome Measures: stent failure rate, incidence of AD post-stent placement, complications.</td>
<td>1. 33 stents were placed in 28 patients. 2. 6 patients reported severe autonomic dysreflexia related to poor bladder emptying as their reason for stent placement. 3. Severe AD decreased significantly from 17 cases before stent placement to 7 after stent placement. 4. New severe AD was a complication of stent placement in one case, after which the stent was removed.</td>
</tr>
<tr>
<td>Ke &amp; Kuo 2010; Taiwan</td>
<td>Case series</td>
<td>N=22</td>
<td>Population: 19 males; 13 subjects with cervical SCI, 9 with thoracic SCI. 17 subjects reported AD. Mean age at diagnosis of BND = 46.7 years. Lower urinary tract symptoms experienced for mean of 3.8 years. Treatment: transurethral incision of the bladder neck (TUI-BN). Outcome Measures: urodynamic parameters; satisfactory outcome (increase of AUA/IPSS quality-of-life index score by ≥2); autonomic dysreflexia occurrence; spontaneous voiding; detrusor pressure; post void residual; Qmax; bladder outlet resistance.</td>
<td>1. Spontaneous voiding resumed in 19 patients, persistent urinary retention in 3 patients. 2. Urodynamic parameters: For patients with a Pdet &gt; 15cmH2O at baseline, after surgery: Pdet and Qmax increased, PVR decreased, Qmax increased, PVR decreased significantly from 3.7(5.7) to 8.3(5.4)mL/sec; For patients with a Pdet ≤15cmH2O at baseline, after surgery: Pdet and Qmax increased, PVR decreased significantly from 369(160) to 117(136)mL. 3. Degree of AD during micturition was less severe or disappeared in 15 patients (88.2%) after surgery. 4. 18 (82%) patients reported satisfactory improvement in QoL index after TUI-BN, and voiding by volitional drills or lower abdominal tapping maneuvers became easier.</td>
</tr>
<tr>
<td>Perkash 2007; USA</td>
<td>Case series</td>
<td>N=46</td>
<td>Population: 46 males; 31 subjects with tetraplegia and 15 with paraplegia; Type of injury: 43 AIS A and B, 3 AIS C. Treatment: Transurethral sphincterotomy (TURS). Outcome Measures: Autonomic</td>
<td>1. During cystometrogram, mean maximal systolic pressure was 160(23) pre and 108(17) mmHg post. Mean diastolic pressure was 88(15) pre and 62(11) mmHg post. 2. Mean decrease in systolic BP and diastolic BP after TURS was 55(26) and 30(17) mmHG, respectively.</td>
</tr>
</tbody>
</table>
### Author Year; Country Score Research Design Sample Size

**Methods**

dysreflexia during cystometrogram (measures the contractile force of the bladder when voiding), blood pressure.

**Outcome**

3. Amelioration in symptoms of AD.
4. Mean post-void residual urine decreased significantly from 233(152) to 137(0.35) mL after TURS.
5. 4 patients still exhibited AD within 1 year of laser TURS.

---

**Population:** 47 males; 32 subjects with cervical, 11 with thoracic, and 4 with lumbar injuries; mean post-injury time to stenting was 103.8 months. Mean follow-up time from implantation 67 months. Type of injury: 36 AIS A; 4 AIS B and 7 AIS C.

**Treatment:** intraurethral stent.

**Outcome Measures:** Urodynamic parameters; presence or absence of symptomatic UTI; autonomic dysreflexia; appearance of complications of the upper urinary tract (UUT); bladder management before and after surgery; prosthesis complications.

1. Decrease in symptomatic UTI by 25%.
2. Decrease in post void residual urine volume by an average of 224.3 cm³.
3. Episodes of dysreflexia decreased from 35.1% to 16.2%.
4. Complications in the UUT decreased from 46.8 to 23.4%.
5. Urodynamic study showed an average reduction of 44.4 cm³ H2O in the maximum detrusor pressure.
6. Most frequent stent complication was displacement, followed by stenosis, lithiasis (pathological formation of mineral concentrations in the body), and intraprosthetic calcification. 8.5% required stent removal.

---

**Population:** 9 subjects with complete SCI, 3 with incomplete injuries; Level of Injury: C5-T11; 2-27 years post-injury.

**Treatment:** augmentation enterocystoplasty.

**Outcome Measures:** functional bladder capacity, levels of blood urea nitrogen, creatinine, electrolytes.

1. By 4 months post-op, 11/12 patients were totally continent on clean intermittent self-catheterization every 4-6 hours.
2. Of the 3 patients who had an artificial urinary sphincter, 2 became continent after sphincter activation and 1 had achieved continence without sphincter activation. No patients experienced symptoms of AD during intermittent catheterization post-operatively.

---

**Population:** 5 subjects with thoracic, and 8 with cervical injuries, 47-285 months post-injury.

**Treatment:** modified transurethral external sphincterotomy with follow-up to 26 weeks.

**Outcome Measures:** bladder and urethral pressures and volumes, blood pressures.

1. Intravesical and urethral pressures decreased compared to before sphincterotomy.
2. Blood pressure responses decreased during urodynamic stimulation.
3. Other cardiovascular responses related to AD during bladder filling markedly attenuated.

---

### Discussion

Four surgical studies (Barton et al. 1986; Sidi et al. 1990; Perkash 2007; Ke & Kuo 2010) included indicators of AD (e.g., blood pressure changes). An older study by Barton et al. (1986) demonstrated reduced AD with an external sphincterotomy. A long-term follow-up of patients treated with transurethral sphincterotomies showed the procedure provided subjective relief of AD and was correlated with a significant decrease in blood pressure (Perkash 2007). Additionally, post-void residual urine decreased significantly after surgery (Perkash 2007). Similar results were found by Ke & Kuo in 2010. Patients reported decreased severity in the degree of AD during micturition, as well as significant decrease of post-void residual urine and improvement in quality of life (QoL) index after bladder surgical augmentations.
Sphincterotomies are now rarely performed due to their association with significant risks, including hemorrhage, erectile dysfunction (Ahmed et al. 2006) and the need for repeat procedures (Secrest et al. 2003). Alternatives including intraurethral stents and Botulinum toxin injections have been investigated and shown some success (Ahmed et al. 2006; Seoane-Rodriguez et al. 2007; Pannek et al. 2011; van der Merwe et al. 2012). Augmentation enterocystoplasty has demonstrated long-term success based on urodynamic evaluation and has been found to reduce symptoms of AD (Sidi et al. 1990). Enterocystoplasty with a Mitrofanoff procedure has become a more frequent choice of bladder augmentation in individuals with SCI due to more favorable long-term outcomes. Memokath stent placement in the external sphincter region has demonstrated a significant reduction in post-void residual urine as well as in UTI symptoms (Pannek et al. 2011; van der Merwe et al. 2012). Dual flange Memokath stent placement over the internal and external urethral sphincters in 28 patients with neuropathic bladder dysfunction was shown by van der Merwe et al. (2012) to reduce severe AD from 17 cases to 7 cases after stent placement.

**Conclusion**

*There is level 4 evidence (based on four pre-post/case series studies) (Barton et al. 1986; Sidi et al. 1990; Perkash 2007; Ke & Kuo, 2010) that urinary bladder surgical augmentations may result in a decrease of intravesical and urethral pressure and therefore diminish or resolve episodes of AD.*

*There is level 4 evidence (based on 2 case series) (van der Merwe et al. 2012; Seoane-Rodriguez et al. 2007) that an intraurethral stent decreases incidence of AD and may be an effective means for the long-term management of detrusor-sphincter dysynergia for SCI patients, including those who have previously undergone sphincterotomy.*

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**5.2 Prevention of AD during Anorectal Procedures**

The second most common cause of AD is pain or irritation within the colorectal area. Constipation, hemorrhoids, and anal fissures, all frequently observed in patients with SCI, contribute to episodes of AD (Teasell et al. 2000; McGuire & Kumar 1986; Hawkins et al. 1994; Teichman et al. 1998). Digital stimulation, a common component of bowel routines in individuals with SCI, can also trigger AD (Furusawa et al. 2007), especially in the presence of hemorrhoids and/or anal fissures. In addition, rectosigmoid distension and anal manipulation are common iatrogenic triggers of AD (Cosman & Vu 2005).

**Table 8: Prevention of AD during Anorectal Procedures**

<table>
<thead>
<tr>
<th>Author Year; Country Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosman &amp; Vu 2005; USA PEDro=11 RCT N=25</td>
<td><strong>Population:</strong> All subjects with complete SCI; age 46-49 years; 15-25 years post-injury; level of injury: C4-T1 <strong>Treatment:</strong> intersphincteric anal block with either: a) 300 mg 1% lidocaine or b) normal saline (placebo) before sigmoidoscopy or anoscopy hemorrhoid ligation procedure. <strong>Outcome Measures:</strong> blood pressure.</td>
<td>1. The mean maximal systolic blood pressure increase for the lidocaine group (22(14) mmHg) was lower than the placebo group (47(31) mmHg) suggesting that AD risk was reduced with lidocaine.</td>
</tr>
</tbody>
</table>
### Author Year; Country Score

<table>
<thead>
<tr>
<th>Research Design</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosman et al. 2002; USA PEDro=9 RCT N=45</td>
<td></td>
</tr>
</tbody>
</table>

#### Methods

**Population:** 45 patients (44 male, 1 female) with chronic, complete SCI, injury level of T6 or above, undergoing anoscopy and/or flexible sigmoidoscopies.

**Treatment:** a) 2% topical lidocaine jelly (n=18) or; b) nonmedicated lubricant (control, n=32) just prior to the procedure.

**Outcome Measures:** blood pressure.

1. Topical lidocaine had no significant effect on mean maximal systolic blood pressure (increased 35(25) mmHg in the lidocaine group vs. 45(30) mmHg in the control group).
2. Greater SBP increase with anoscopic procedure compared to sigmoidoscopic procedures (49(29) vs. 25(20) mmHg, respectively).

| Furusawa et al. 2009; Japan PEDro=8 RCT N=25 |

#### Methods

**Population:** 25 cervical SCI subjects (22 men, 3 women); Level of injury: C4-C7; mean(SD) time post-injury: 23.4(36.4), range 3-172 months.

**Treatment:** 10mL of 2% Lidocaine treatment group (placebo jelly for control group); both groups then underwent digital bowel stimulation to initiate and augment stool flow.

**Outcome Measures:** blood pressure; heart rate; symptoms of autonomic dysreflexia.

1. 10 subjects in the control group reported symptoms of AD, compared to 4 patients in the treatment group.
2. Systolic blood pressure was significantly lower in treatment group, compared to the control.
3. No significant difference in diastolic blood pressure or heart rate.

### Discussion

In two small RCTs (n=70) (Cosman & Vu 2005; Cosman et al. 2002), investigators compared the effect of topical local anesthesia of the anorectal area to a nonmedicated control gel for the prevention of AD during anorectal procedures. They found that anoscopy, which involves stretching the anal sphincters, was a more potent stimulus for AD than flexible sigmoidoscopy, which involves gaseous distention of the rectosigmoid. In one randomized, double-blind, placebo-controlled trial, AD was not abolished by topical lidocaine in the rectum during the anorectal procedure (Cosman et al. 2002). However, the same investigators in a later RCT demonstrated that intersphincteric anal block with lidocaine was effective in limiting anorectal procedure-associated AD (Cosman et al. 2002). In one small RCT (n=25) (Furusawa et al. 2009) investigators found that topical lidocaine applied to the rectum prior to digital bowel stimulation significantly reduced systolic blood pressure and reports of AD over the duration of the bowel program when compared to the control group.

### Conclusion

**There is level 1 evidence (from 1 RCT) (Cosman & Vu 2005) that lidocaine anal block significantly limits the AD response in susceptible patients undergoing anorectal procedures.**

**There is level 1 evidence (from 1 RCT) (Cosman et al. 2002) that topical lidocaine does not limit or prevent AD in susceptible patients during anorectal procedures.**

**There is level 1 evidence (from 1 RCT) (Furusawa et al. 2008) that topical lidocaine may help to prevent AD during gentle bowel stimulation.**

Lidocaine anal block can limit the AD response in susceptible patients undergoing anorectal procedures.

Topical lidocaine may prevent AD during digital bowel stimulation but does not prevent AD during anorectal procedures.
5.3 Prevention of AD during Pregnancy and Labour

In North America, women represent a third of the SCI population (Ackery et al. 2004). Approximately 3,000 American women of childbearing age are affected by SCI (Cross et al. 1992). The ability of women to have children is not usually affected by SCI once their menstrual cycle resumes (Jackson & Wadley 1999). There are increasing numbers of women with SCI who have healthy babies (Cross et al. 1992). However, during labour and delivery, susceptible women with SCI are at high risk of developing uncontrolled AD (Sipski 1991; Sipski & Arenas 2006). Recognition and prevention of this life threatening emergency is critical for managing labour in women with SCI (McGregor & Meeuwsen 1985). The majority of women with SCI above T10 experience uterine contractions as only abdominal discomfort, an increase in spasticity and AD (Hughes et al. 1991).

Table 9: Prevention of AD during Pregnancy and Labour

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skowronski &amp; Hartman 2008; Australia</td>
<td>N=5</td>
<td>Case series</td>
<td>Population: 5 females with tetraplegia who gave birth a total of 7 times (two subjects gave birth twice). Treatment: N/A</td>
<td>Outcome Measures: Complication, management, and outcomes of pregnancy; hospital records.</td>
<td>1. AD occurred in 6 of 7 pregnancies. 2. AD was managed pre-emptively by insertion of an epidural either before or in the early stages of labour, with generally good results 3. Dangerously high peaks were managed by the administration of either sublingual nifedipine or intramuscular clonidine. 4. Other major complications include urinary tract infection (present in all pregnancies) and muscle spasms (4 of 7 pregnancies).</td>
</tr>
<tr>
<td>Cross et al. 1992; USA</td>
<td>N=22</td>
<td>Case series</td>
<td>Population: 22 women with SCI, 11 with cervical and 11 with thoracic injuries; 10 with incomplete and 12 with complete injuries. Treatment: epidural anesthesia.</td>
<td>Outcome Measures: presence of autonomic hyperreflexia, type of anesthesia, type of delivery, complications.</td>
<td>1. AD was experienced in 9/16 &gt; T6. 2. One patient had two grand mal seizures during labour, which may have been triggered by her severe AD and the subsequent intravenous administration of diazepam. 3. Six patients had epidural anesthesia, which was effective for the control of AD.</td>
</tr>
<tr>
<td>Cross et al. 1991; USA</td>
<td>N=16</td>
<td>Observational</td>
<td>Population: 7 subjects with cervical and 9 with thoracic injuries. Treatment: questionnaire (in person or telephone) and hospital records review.</td>
<td>Outcome Measures: outcomes of pregnancies.</td>
<td>1. Of the 16 women, 25 pregnancies occurred, resulting in 22 babies and 3 abortions. 2. 2/15 vaginal deliveries and 5/7 Caesarean section had AD during delivery with 4 of these receiving epidural anesthesia for the control of AD. 3. 1 patient required epidural catheter 5 days postpartum to control AD.</td>
</tr>
<tr>
<td>Hughes et al. 1991; UK</td>
<td>N=15</td>
<td>Observational</td>
<td>Population: 17 pregnancies in 15 women with SCI, level of injury: T4-L3. Treatment: management and outcome of pregnancies in women with SCI.</td>
<td>Outcome Measures: antenatal care and problems, labour diagnosis and outcome.</td>
<td>1. Labour tended to be diagnosed by dysreflexic symptoms or membrane rupture with confirmation by palpation of contractions and vaginal examination. 2. Initial management of AD included elevation of head of the bed, nifedipine and nitrates. 3. The most effective measure for controlling AD was to identify and interrupt the triggering afferent input to the spinal cord.</td>
</tr>
<tr>
<td>Ravindran et al. 1981; USA</td>
<td>N=1</td>
<td>Case report</td>
<td>Population: 19 yr-old female with C5 complete tetraplegia admitted to the obstetrical intensive care unit for intra-amniotic prostaglandin F2-alpha</td>
<td></td>
<td>1. 100 mg/min of sodium nitroprusside decreased SBP from 170 mmHg to 120 mmHg caused by vaginal speculum introduction.</td>
</tr>
</tbody>
</table>
### Discussion

Numerous observational studies, case reports and expert opinions recommend adequate anesthesia in women with SCI during labour and delivery despite the apparent lack of sensation. However, there are only five studies (n=59) (Cross et al. 1992; Hughes et al. 1991; Cross et al. 1991; Ravindran et al. 1981; Skowronski & Hartman 2008) with observational evidence recording the management specific to AD during labour. The American College of Obstetrics and Gynecology emphasized that it is important that obstetricians caring for these patients be aware of the specific problems related to SCI (American College of Obstetrics and Gynecology 2002).

### Conclusion

*There is level 4 evidence that women with SCI may safely give birth vaginally. With vaginal delivery or when Caesarean delivery or instrumental delivery is indicated, adequate anesthesia (spinal or epidural if possible) is needed to reduce the episodes of AD associated with birth.*

*There is level 4 and 5 evidence (from 2 case series and 2 observational studies) (Cross et al. 1992; Hughes et al. 1991; Cross et al. 1991; Showronski and Hartman 2008) that epidural anesthesia is preferred and effective for most patients with AD during labour and delivery.*

Adequate anesthesia (spinal or epidural if possible) is needed with vaginal delivery, Caesarean delivery or instrumental delivery. Epidural anesthesia is preferred and effective for most women with AD during labour and delivery.

### 5.4 Prevention of AD during General Surgery

Despite the partial or total loss of sensation below the level of injury, surgical procedures or manipulations can potentially initiate episodes of AD. Anesthesiologists and surgeons performing surgery on SCI patients must be aware of the interactions of the anesthetic and its effects on AD and how to prevent or manage AD during these procedures.
Table 10: Prevention of AD during Surgery

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Research Design</th>
<th>Sample Size</th>
<th>Population</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eltorai et al. 1997; USA</td>
<td>Observational</td>
<td>N=591</td>
<td>Level of injury: C1-T10, mean length of injury: 22.3 yrs.</td>
<td>AD occurred most commonly during the start of anesthesia (induction) with the greatest frequency when no anesthesia was provided.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: retrospective review of anesthetic methods during surgery.</td>
<td>During induction, systolic blood pressure increased in 68.7% of procedures during combined local anesthesia and intravenous (IV) sedation, in 65.4% of IV sedation alone, in 62.1% of local anesthesia alone, in 51.5% of spinal or epidural anesthesia, in 51.5% of general anesthesia, and in 88.8% of no anesthesia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome Measures: blood pressure.</td>
<td>1. During induction, systolic blood pressure increased in 68.7% of procedures during combined local anesthesia and intravenous (IV) sedation, in 65.4% of IV sedation alone, in 62.1% of local anesthesia alone, in 51.5% of spinal or epidural anesthesia, in 51.5% of general anesthesia, and in 88.8% of no anesthesia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Intraoperatively systolic BP increased significantly by 37 mmHg in patients receiving topical or no anesthesia. No significant difference in BP changes between general and spinal anesthesia groups.</td>
<td></td>
</tr>
<tr>
<td>Lambert et al. 1982; USA</td>
<td>Observational</td>
<td>N=50</td>
<td>Subjects had injuries that were above T6, and complete; mean of 6.5 years post-injury.</td>
<td>Intraoperative hypertension occurred more significantly with topical or no anesthesia (15/19) compared to general anesthesia (3/13) or spinal anesthesia (3/46).</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: Retrospective review of 78 procedures. Three groups: 1) topical or no anesthesia sedation (n=19), 2) general anesthesia (n=13), and; 3) spinal anesthesia (n=46).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome Measures: blood pressure.</td>
<td>2. Intraoperatively systolic BP increased significantly by 37 mmHg in patients receiving topical or no anesthesia. No significant difference in BP changes between general and spinal anesthesia groups.</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Two observational studies (Lambert et al. 1982; Eltorai et al. 1997) presented evidence that AD is a common complication during general surgery in individuals with SCI. Up to 90% of individuals undergoing surgery with topical anesthesia or no anesthesia developed AD. Both studies concluded that patients at risk for AD could be protected by either general or spinal anesthesia.

Conclusion

There is level 5 evidence (from 2 observational studies) (Lambert et al. 1982; Eltorai et al. 1997) that indicates that patients at risk for autonomic dysreflexia are protected from developing intraoperative hypertension by either general or spinal anesthesia.

Anesthesiologists and surgeons dealing with SCI patients must know how to recognize the AD syndrome, how to prevent its occurrence and how to manage it.

Anesthesia should be used during surgical procedures in individuals with SCI despite apparent lack of sensation.

5.5 Prevention of AD during FES Exercise

Functional electrical stimulation (FES) is a widely-used modality in the rehabilitation of individuals with SCI (Sampson et al. 2000; Wood et al. 2001). Similar to any non-noxious or noxious stimuli below the level of injury, FES itself may also lead to significant afferent stimulation and trigger the development of AD (Ashley et al. 1993; Matthews et al. 1997).
Table 11: Prevention of AD during FES Exercise

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthews et al. 1997; Canada</td>
<td>PEDro=7</td>
<td>RCT</td>
<td>N=7</td>
<td><strong>Population:</strong> Injury level: C4-C7; all injuries were complete; age range: 23-44 years; 3-21 years post-injury. <strong>Treatment:</strong> Randomized to: a) topical anesthetic or: b) placebo creams applied to the quadriceps muscles during graded FES exercise. <strong>Outcome Measures:</strong> heart rate, blood pressure, serum catecholamines.</td>
<td>1. No differences in HR, BP or catecholamine responses or FES force were seen between the two conditions.</td>
</tr>
</tbody>
</table>

Discussion

One RCT (n=7) assessed the effect of topical anaesthetic and placebo creams applied to the skin area over the quadriceps muscle 1 hour prior to FES on two different days (Matthews et al. 1997). As cardiovascular and AD responses during FES were unaffected by topical anaesthetic cream application at the stimulation site, the authors suggested that mechanisms other than skin nociception contributed to FES-induced AD.

Conclusion

*There is level 1 evidence (from one RCT) (Matthews et al. 1997) supporting no effect of topical anesthetic for the prevention of AD during FES.*

Topical anesthetic is not effective for the prevention of AD during FES.

5.6 Prevention of AD with Stoma

Neurogenic bowel dysfunction is increasingly recognized as a major barrier to increasing quality of life in people with SCI. Bowel management difficulties include constipation, abdominal pain, faecal incontinence, prolonged transit time, and AD. The treatment of neurogenic bowel dysfunction with stoma usually takes place when other interventions such as transanal irrigation, pharmacological agents, etc. have failed.

Table 12: Prevention of AD with Stoma

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coggrave et al. 2012; UK</td>
<td>Cross-sectional</td>
<td>N=92</td>
<td></td>
<td><strong>Population:</strong> 92 subjects with SCI and stoma (64M, 28F); mean (SD) age in yrs: 56(9), range 24-86; mean (SD) age at injury (yrs): 30(13), range 6-64; 26 cervical (15 complete, 10 incomplete, 1 unknown), 61 thoracic (49 complete, 10 incomplete, 2 unknown), 1 missing data on level of injury; 91% colostomy, 9% ileostomy. <strong>Treatment:</strong> Retrospective analysis of a self-report postal survey of individuals with SCI who had a stoma.</td>
<td>1. 19 respondents reported autonomic dysreflexia as their reason for stoma surgery. 2. Autonomic dysreflexia associated with bowel management was reported by significantly fewer respondents following stoma surgery (37% before, 18% after stoma formation).</td>
</tr>
</tbody>
</table>
## Discussion

One cross-sectional study (n=92) completed a retrospective analysis participants who had stomas. Following stoma surgery, significantly fewer respondents reported AD associated with bowel management (37% before, 18% after).

## Conclusion

**There is level 4 evidence (Coggrave et al. 2012) that AD associated with bowel management decreases following stoma surgery.**

### 5.7 Prevention of AD in Acute Care

The primary mechanisms of SCI are irreversible, therefore, prevention of AD in acute care are mainly focused on the attenuation of the effects of secondary injuries which are delayed, prolonged, and reversible.

### Table 13: Prevention of AD in Acute Care

<table>
<thead>
<tr>
<th>Author Year; Country Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. 2012; China Pre-Post (Multiple Groups) N=295</td>
<td><strong>Population:</strong> 295 adults who underwent surgical decompression for acute traumatic SCI; mean (SD) age in yrs: 42.11(13.75); sex (ratio): 1.63:1 (male: female); preoperative AIS: A (n=135), B (n=29), C (n=36), D (n=95); preoperative ASIA motor index total score: 42.64(27.02); preoperative motor score of injured level: 4.02(0.46); preoperative sensory score of injured level: 3.02(0.45). <strong>Treatment:</strong> cases were extracted and assigned into 3 groups on the basis of the timing of surgery: Urgent group (n=99, within 8 h after injury), Early group (n=86, from 8h to 48 h after injury), Delayed group (n=110, after 48 h); neurological outcomes and medical complications were compared before the operation, after the operation, at 6 months, and at 1 year. <strong>Outcome Measures:</strong> ASIA motor index total score; ASIA Impairment Scale (AIS); Motor and sensory scores of injured level; medical complications.</td>
<td>1. Deep vein thrombus (DVT), hypostatic pneumonia, autonomic dysreflexia, and pressure ulcers were the most commonly seen medical complications of surgical decompression. 2. Morbidity of autonomic dysreflexia increased with time because of delayed injuries; it was still lower in the urgent and the early groups than in the delayed group, because urgent and early surgical decompression blocked secondary injury mechanisms in time. 3. Urgent and early surgical decompression lowered the increase in the morbidity of autonomic dysreflexia more effectively than delayed surgical decompression. (Post-operatively: urgent=5.9%; early=5.4%; delayed=9.7%. At 6 months: urgent=5.7%; early=5.3%; delayed=9.7%)</td>
</tr>
</tbody>
</table>
Discussion
One prospective study (Chen et al. 2012, n=295) examined differences in morbidity of AD in patients with acute SCI treated with surgical decompression at different times (urgent, early and delayed). The study found that patients in the urgent and early surgical decompression groups had lower AD incidence post-operatively and at 6 months follow-up.

Conclusion
There is level 4 evidence from one prospective study (Chen et al. 2012) that earlier surgical decompression after acute SCI results in decreased AD incidence as compared to delayed surgical compression.

6.0 Management of Acute AD Episodes
Despite appropriate preventative strategies, AD remains common among individuals with SCI. As previously noted, especially in individuals with cervical or high thoracic injuries, episodes of AD, even accompanied by a significant increase in arterial blood pressure, can be asymptomatic (Linsenmeyer et al. 1996; Ekland et al. 2007; McGillivray et al. 2006). The Guidelines of the Consortium for Spinal Cord Medicine for management of AD recommends employing non-pharmacological measures initially; if they fail, and systolic blood pressure continues to be at or above 150 mmHg in adults, 120 mmHg in children under 5 years old, 130 mmHg in children 6-12 years old, and 140 mmHg in adolescents, pharmacological agents should be initiated (Consortium for Spinal Cord Medicine 2006).

6.1 Non-Pharmacological Management of AD
The initial management of an episode of AD involves placing the patient in an upright position to take advantage of an orthostatic reduction in blood pressure (Consortium for Spinal Cord Medicine 2001). While there are no studies that evaluate the effect of a sit-up position on blood pressure during the episodes of AD, significant decreases in resting blood pressure have been shown during a tilt or sit-up test from supine position in individuals with SCI (Claydon & Krassioukov 2006; Krassioukov & Harkema 2006; Sidorov et al. 2007). It is proposed that an upright posture will induce pooling of blood into the abdominal and lower extremity vessels as peripheral vasoconstriction is compromised or lost following SCI; thus arterial blood pressure is reduced. The next step is to loosen any tight clothing and constrictive devices (Consortium for Spinal Cord Medicine 2001). This procedure will also allow more blood to pool into the vessel beds below the level of injury as well as removal of a possible trigger of peripheral sensory stimulation. Blood pressure should be checked at a minimum of 5 minute intervals until the individual is stable (Consortium for Spinal Cord Medicine 2001), at which time it is necessary to search for and eliminate the precipitating stimulus, which in 85% of cases can be found to relate to either bladder distention or bowel impaction (Teasell et al. 2000; Mathias & Bannister 2002). The use of antihypertensive drugs should be considered as a last resort and used if the systolic blood pressure remains at 150 mmHg or greater following the steps outlined above (Consortium for Spinal Cord Medicine 2001). The goal of such an intervention is to alleviate symptoms and avoid the complications associated with uncontrolled hypertension (Yarkony et al. 1986; Pine et al. 1991; Eltorai et al. 1992; Valles et al. 2005).

6.2 Pharmacological Management of AD
Episodes of AD in individuals with SCI can vary in severity, but in some cases can be asymptomatic and be managed by the individual once they are familiar with their own triggers and symptoms (Linsenmeyer et al. 1996). However, in some individuals it is difficult to find the trigger for the acute blood pressure elevation and immediate medical attention is required (Elliott & Krassioukov 2006). Antihypertensive drugs with a rapid onset and short duration of action should be used in the management of acute episodes (Blackmer 2003). The Consortium for Spinal Cord Medicine recommends that if non-pharmacological measures fail and arterial blood pressure remains 150 mmHg or greater, pharmacological management should be initiated (Consortium for Spinal Cord Medicine 2006).
However, the Consortium for Spinal Cord Medicine (2001) does not identify any particular medication for management of AD. Numerous pharmacological agents (e.g., nifedipine, nitrates, captopril, terzaosin, prazosin, phenoxybenamine, Prostaglandin E2, sildenafil) have been proposed for management of episodes of AD (Consortium for Spinal Cord Medicine; Blackmer 2003; Naftchi & Richardson 1997). The majority of the recommendations are based on the clinical management of hypertensive crises in able-bodied populations, as well as case reports and anecdotal evidence. Characteristics and outcomes of studies assessing pharmacological interventions for the management of AD are presented in the following sections.

The literature supporting pharmacological management of AD using fast-acting antihypertensive drugs is specific to SCI. Although the use of fast-acting anti-hypertensives is strongly discouraged in able-bodied populations, there is a clinical need for immediate action in individuals with SCI, due to the mechanisms of hypertensive crisis and a result of the emergent risk of intracranial bleed, myocardial infarction or death (Ho & Krassioukov 2010; Yoo et al. 2010). Episodes of AD are typically short lasting events, and could thus be well controlled with the use of short acting antihypertensive medications. Therefore, the use of these medications at a low dose and only as needed is less likely to result in the deleterious effects observed in the able bodied population when initially prescribed for the management of hypertension.

### 6.2.1 Nifedipine (Adalat, Procardia)

Nifedipine, a calcium ion influx inhibitor (Ca-channel blocker), selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle while maintaining serum calcium concentrations. In humans, Nifedipine decreases peripheral vascular resistance and creates a modest fall in systolic and diastolic pressure (5-10mm Hg systolic although sometimes larger). Nifedipine is generally given using the "bite and swallow" method, in a dose of 10 mg.

<table>
<thead>
<tr>
<th><strong>Table 14: Nifedipine (Adalat, Procardia)</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Author Year; Country</strong></td>
</tr>
<tr>
<td><strong>Score Research Design Sample Size</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Thyberg et al. 1994; Sweden Pre-post N=10</td>
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<tr>
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<tr>
<td>Kabalin et al. 1993; USA Case series N=20</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Author Year; Country</td>
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<tr>
<td>----------------------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Dykstra et al. 1987;</td>
</tr>
<tr>
<td>Lindan et al. 1985;</td>
</tr>
<tr>
<td>Prospective controlled trial</td>
</tr>
</tbody>
</table>

**Outcome Measures:**
- blood pressure, voltage and current delivered during electroejaculation.

**Population:** Subjects with complete, cervical injuries.

**Treatment:** 10 mg nifedipine during cystoscopy procedure.

**Outcome measures:** blood pressure, presence of AD.

**Population:** 12 subjects with tetraplegia.

**Treatment:** phenoxybenzamine (10mg bid) versus nifedipine (20mg bid) administration at least 4 days prior cystometry. 11 patients were also tested for the efficacy of 10 mg nifedipine (sublingually or by mouth) for controlling AD symptoms.

**Outcome Measures:** blood pressure.

1. Neither drug prevented AD secondary to bladder filling, and a significant number of patients developed hypotension.
2. Sublingual dose of nifedipine (10 mg) was effective in managing acute attacks of AD.

**Discussion**

Five studies (n=59) (Steinberger et al. 1990; Lindan et al. 1985; Thyberg et al. 1994; Kabalin et al. 1993; Dykstra et al. 1987) have evaluated the effects of Nifedipine; two level 2 controlled but not randomized trials (Steinberger et al. 1990; Lindan et al. 1985), and three level 4 studies (Thyberg et al. 1994; Kabalin et al. 1993; Dykstra et al. 1987). Four of these five studies saw a reduction or alleviation of AD with nifedipine (Steinberger et al. 1990; Thyberg et al. 1994; Kabalin et al. 1993; Dykstra et al. 1987). In their non-randomized control trial, Steinberger and co-investigators (1990) reported that sublingual nifedipine decreased peak systolic, diastolic, and mean blood pressure in SCI individuals undergoing electroejaculation. Braddom and Rocco (1991) surveyed 86 physicians with an average of 16.8 years of experience in managing AD in patients with SCI. While pharmacologic treatment of AD varied greatly from physician to physician, antihypertensive medications were the most frequently used medications with Nifedipine being a drug of choice for 48% of physicians for minor AD cases and for 58% of physicians for severe symptomatic AD cases. Although nifedipine has been the most commonly used agent for management of AD in individuals with SCI (Thyberg et al. 1994; Dykstra et al. 1987; Esmail et al. 2002; Braddom & Rocco 1991), its use has declined recently (Frost 2002; Anton & Townson 2004). There have been no reported adverse events from the use of nifedipine in the treatment of AD (Blackmer 2003), although all studies had a very small sample size. However, a review of nifedipine for the management of hypertensive emergencies not specific to SCI found serious adverse effects such as stroke, acute myocardial infarction, death and numerous instances of severe hypotension (Grossman et al. 1996). Due to several reports of serious adverse reactions occurring after administration of immediate-release nifedipine, the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (1997) has discouraged use of this drug.

**Conclusion**

There is level 2 evidence (from 2 prospective controlled trials) (Steinberger et al. 1990; Lindan et al. 1985) that Nifedipine may be useful to prevent dangerous blood pressure reactions, e.g. during cystoscopy and other diagnostic or therapeutic procedures in SCI injured patients with AD.
There is level 5 evidence (from clinical consensus) (Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure 1997), that serious adverse effects from Nifedipine may occur and these have been reported in other populations.

Nifedipine may be useful to prevent or control AD in SCI individuals; however, serious adverse effects from may occur similar to those reported in other populations.

6.2.2 Nitrates (Nitroglycerine, Depo-Nit, Nitrostat, Nitrol, Nitro-Bid)

Nitrates are used for the management of an acute episode of AD as they relax vascular smooth muscle, thus producing vasodilator effects on peripheral arteries and veins. Dilation of post-capillary vessels, including large veins, promotes peripheral pooling of blood and reduces venous return to the heart, thereby reducing left ventricular end-diastolic pressure (pre-load) and arterial blood pressure. On the other hand, arteriolar relaxation reduces systemic vascular resistance, which leads to reduced arterial pressure (after-load). If sildenafil has been used within the previous 24 hours in an individual with SCI presenting with acute AD, use of an alternative short acting, rapid-onset antihypertensive agent is recommended. Nitrates are the second most commonly used agent after nifedipine for management of AD in individuals with SCI (Consortium for Spinal Cord Medicine 2001; Braddom & Rocco 1991). However, with the exception of one case report with intravenous use of nitroprusside (Ravindran et al. 1981) and expert opinions (Consortium for Spinal Cord Medicine 2001), no studies exist to support their use in SCI.

Discussion

There is level 5 evidence (clinical consensus) (Consortium for Spinal Cord Medicine 2001; Braddom & Rocco 1991), but no clinical studies which support the use of nitrates in the acute management of AD in SCI.

Conclusion

There is level 5 evidence (clinical consensus) (Consortium for Spinal Cord Medicine 2001; Braddom & Rocco 1991), but no clinical studies which support the use of nitrates in the acute management of AD in SCI.

Nitrates are commonly used in the control of AD in SCI; however, no studies have been done to show their effectiveness or safety in SCI.

6.2.3 Captopril

Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE). During an episode of AD, 25mg of captopril is recommended for sublingual administration.

Table 15: Captopril

<table>
<thead>
<tr>
<th>Author Year; Country Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmail et al. 2002; Canada Pre-post N=7</td>
<td><strong>Population:</strong> 26 consecutive patients older than 15 years with SCI above T6. <strong>Treatment:</strong> administration of a) captopril 25mg sublingually if systolic blood</td>
<td>1. A total of 33 autonomic dysreflexia episodes were documented in 7 patients. 2. The 18 episodes documented in 5 patients were treated with drug therapy.</td>
</tr>
</tbody>
</table>
pressure (SBP) was at or above 150mmHg, b) 5mg of immediate-release nifedipine if SBP remained elevated 30 minutes after captopril administration. **Outcome Measures:** SBP

3. Captopril alone was effective in reducing SBP in 4 of 5 the patients (80%). The mean SBPs at baseline and 30 minutes after captopril were 178(18) mmHg and 133(28)mmHg, respectively.
4. The addition of nifedipine successfully reduced blood pressure from 170/108 to 110/80 after 30 minutes in the one patient who did not respond to the administration of captopril.

**Discussion**

From one pre-post study (n=26) (Esmail et al. 2002), captopril was safe and effective in 4 out of 5 episodes for AD management. This prospective open labeled study and numerous experts’ opinion suggest the use of the captopril as a primary medication in management of AD (Consortium for Spinal Cord Medicine 2001; Frost 2002; Anton & Townson 2004).

**Conclusion**

*There is level 4 evidence (from one pre-post study) (Esmail et al. 2002) for the use of captopril in the acute management of AD in SCI.*

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**Preliminary evidence suggests that captopril is effective for the management of AD in SCI.**

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**6.2.4 Terazosin**

Terazosin is a long-acting, alpha-1adrenoceptor selective blocking agent. Selective alpha 1 blockade has been suggested as a good pharmacological choice in the management of AD because of its dual effect at the bladder level (inhibition of urinary sphincter and relaxation of the smooth muscles of blood vessels).

**Table 16: Terazosin**

<table>
<thead>
<tr>
<th>Author Year; Country Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaidyanathan et al. 1998; UK Pre-post N=24</td>
<td><strong>Population:</strong> 18 adults with tetraplegia (17 male, 1 female), 3 children with ventilator-dependent tetraplegia and 3 adult males with paraplegia. All had AD in the absence of an acute factor. <strong>Treatment:</strong> Administration of Terazosin with starting dose of 1 mg (adults) or 0.5 mg (children). Step-wise increments of these doses were given at 3-4 day intervals. <strong>Outcome Measures:</strong> drug-induced hypotension, adverse effects, AD symptoms.</td>
<td>1. The AD symptoms subsided completely with the Terazosin therapy in all the patients. 2. Adult patients required a dose between 1-10 mg and children required between 1-2 mg. 3. The side effects of postural hypotension and drowsiness were transient and mild. One tetraplegic patient developed persistent dizziness and therapy was discontinued.</td>
</tr>
<tr>
<td>Author Year; Country</td>
<td>Methods</td>
<td>Outcome</td>
</tr>
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</tr>
<tr>
<td>Chancellor et al. 1994; USA Pre-post N=21</td>
<td>Population: 21 subjects with complete SCI; injury level C3-T5. Treatment: Terazosin administration. Outcome Measures: blood pressure and autonomic dysreflexia frequency and severity scores</td>
<td>1. Decrease in the AD severity score from baseline at one week, 1 month and 3 months. 2. Degree of muscle spasm and degree of headache did not improve. 3. Decrease in the frequency of AD at 1-week follow-up and was maintained at 1 and 3 months. 4. SBP did not statistically change after 3 months of Terazosin.</td>
</tr>
<tr>
<td>Swierzewski et al. 1994; USA Pre-post N=12</td>
<td>Population: 6 subjects with paraplegia, 6 with quadriplegia. Treatment: nightly Terazosin administration for 4 weeks (5 mg starting dose). Outcome Measures: physical examination, cystoscopy, AD symptoms.</td>
<td>1. Detrusor compliance improved in all patients during the treatment phase. 2. Change in bladder pressure and safe bladder volume were statistically and clinically significant. 3. Terazosine abolished AD in 3 patients and decreased the incidence and the severity of symptoms in 1 patient.</td>
</tr>
</tbody>
</table>

Discussion

Regular doses of Terazosin over weeks or months were evaluated in three level 4 experimental studies (n=57) (Vaidyanathan et al. 1998; Swierzewski et al. 1994; Chancellor et al. 1994) in which it appears to be effective in preventing AD without erectile function impairment. Patients reported moderate to excellent improvement (Chancellor et al. 1994) or even complete termination of the dysreflexic symptoms (Vaidyanathan et al. 1998) during a 3-month period of Terazosin administration.

Conclusion

*There is level 4 evidence (from 3 pre-post studies) (Vaidyanathan et al. 1998; Swierzewski et al. 1994; Chancellor et al. 1994) that regular use of Terazosin may have positive effects on both incontinence and AD.*

6.2.5 Prazosin (Minipress)

Prazosin, a postsynaptic alpha-1 adrenoceptor blocker, lowers blood pressure by relaxing blood vessels. Prazosin has a minimal effect on cardiac function due to its alpha-1 receptor selectivity. The recommended starting dose in adults is 0.5 or 1 milligram (mg) taken two or three times a day.

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krum et al. 1992; Australia PEDro=9</td>
<td>Population: Level of injury: T6 or above, at least 2 episodes of AD in last 7 days.</td>
<td>1. Prazosin was well tolerated and did not significantly lower resting BP. Compared to baseline, the Prazosin group had fewer</td>
</tr>
</tbody>
</table>
RCT
N=15

Treatment: double-blind, randomized to Prazosin 3 mg bid. (n=8) or placebo (n=7) for 2 weeks.
Outcome Measures: frequency and severity of AD, blood pressure.

Discussion
In a small (n=15) (Krum et al. 1992), but high quality RCT, Prazosin twice daily was well tolerated and did not affect the baseline blood pressure; AD episodes were also less severe and shorter in duration over a 2 week period.

Conclusion
There is level 1 evidence (from one RCT) (Krum et al. 1992), that Prazosin is superior to placebo in the prophylactic management of AD.

Discussion
McGuire et al. (1976) reported that hypertension, headache and anxiety of AD could no longer be provoked with bladder filling (but sweating continued to occur) in the six subjects who took phenoxybenzamine (dose range from 10 to 20mg) daily. This result is opposite to Lindan et al’s (1985)
findings. They reported that after taking phenoxybenzamine for 4 or more days, blood pressure still rose with bladder distension in ten subjects and remained at the base level in only two subjects.

**Conclusion**

*There is level 4 evidence (from one pre-post study and one case series study) for use of Phenoxybenzamine in the management of AD; however, the results are conflicting with no effects seen in one study (Lindan et al. 1985) and positive effects in another (McGuire et al. 1976).*

It is not known whether Phenoxybenzamine is effective for the management of AD in SCI.

### 6.2.7 Prostaglandin E2

Prostaglandin E2 is a group of hormone-like substances that contribute to a wide range of body functions including the contraction and relaxation of smooth muscle, the dilation and constriction of blood vessels and control of blood pressure.

**Table 19: Prostaglandin E2**

<table>
<thead>
<tr>
<th>Author Year; Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frankel &amp; Mathias 1980; UK</td>
<td>Prospective controlled trial</td>
<td>N=5</td>
<td>Population: 5 patients with complete SCI; age range: 25-37 years; level of injury: C5-T4, 5-108 months post-injury.</td>
<td>Treatment: trans-rectal electrical ejaculation with and without intravenous administration of Prostaglandin E2. Outcome Measures: heart rate, blood pressure, electrocardiogram.</td>
<td>1. Resting BP decreased and resting HR increased with Prostaglandin E2. 2. BP decreased during electrical stimulation, which enabled tolerance of more intense stimulation and successful ejaculation in 2 patients.</td>
</tr>
</tbody>
</table>

**Discussion**

Frankel and Mathias (1980) studied five subjects; 3 subjects underwent administration with and without Prostaglandin E2 and showed that the level of BP recorded during electrical ejaculation decreased with the drug.

**Conclusion**

*There is level 2 evidence from a very small prospective controlled study (Frankel & Mathias 1980) which used subjects as their own controls and showed that the level of BP recorded during electrical ejaculation was substantially reduced with Prostaglandin E2.*

Prostaglandin E2 is effective for reducing BP responses during electroejaculation.

### 6.2.8 Sildenafil (Viagra)

Sildenafil inhibits phosphodiesterase type 5 (PDE5), relaxes smooth muscle, and increases levels of cGMP in, and inflow of blood to, the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation. The recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity, but it may be taken anywhere from 0.5 hour to 4 hours
before sexual activity. Sildenafil is known to enhance the hypotensive effects of nitrates. Thus, nitrates in any form are contraindicated with sildenafil use.

Table 20: Sildenafil (Viagra)

<table>
<thead>
<tr>
<th>Author Year; Country Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheel et al. 2005; Canada PEDe=5 RCT N=13</td>
<td>Population: 13 males, 8 subjects with cervical and 5 with thoracic injuries. Treatment: oral dose of sildenafil citrate (25-100 mg) or no medication during penile vibratory stimulation. Outcomes Measures: ECG, blood pressure.</td>
<td>1. Sildenafil decreased base BP in cervical SCI. 2. Men with cervical SCI had more pronounced AD during penile vibrostimulation than men with thoracic injuries. 3. Administration of sildenafil had no effect on HR or BP during AD triggered by penile vibratory stimulation in men with SCI.</td>
</tr>
</tbody>
</table>

Discussion
The effect of sildenafil on AD was reported in one small RCT with 13 subjects (Sheel et al. 2005). Although sildenafil decreased resting BP, no effect on magnitude of AD resulting from penile vibrostimulation in men with SCI was observed.

Conclusion
There is level 2 evidence (from 1 RCT) (Sheel et al. 1995) that sildenafil citrate had no effect on changes in BP during episodes of AD initiated by vibrostimulation in men with SCI.

Sildenafil has no effect on AD responses in men with SCI during ejaculation.

6.2.9 Other Pharmacological Agents Tested for Management of AD
While other pharmacological agents have been used to manage AD in individuals with SCI and their use has been reported in the literature (e.g., expert opinion, case report), they currently do not have sufficient evident to warrant recommendation. These include the use of Phenazopyridine for AD associated with cystitis (Paola et al. 2003), magnesium sulfate for AD associated with labour (Maehama et al. 2000) or life-threatening AD in intensive care (Jones & Jones 2002), Diazoxide (Hyperstat) (Erickson 1980) for acute AD episodes and intrathecal baclofen for AD associated with spasticity (Kofler et al. 2009). In addition, there have been reports of the use of beta blockers (Pasquina et al. 1998), Mecamylamine (Inversine) (Braddom & Rocco 1991) and Hydralzine (Apresoline) (Erickson 1980) for the general management of AD symptoms in individuals with SCI.

Table 21: Other Pharmacological Agents Tested for Management of AD

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Evidence</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine (Apresoline)</td>
<td>Expert opinion</td>
<td>Erickson 1980</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Case report</td>
<td>Pasquina et al. 1998</td>
</tr>
<tr>
<td>Mecamylamine (Inversine)</td>
<td>Case report</td>
<td>Braddom &amp; Rocco 1991</td>
</tr>
<tr>
<td>Magnesium sulphate</td>
<td>Case report</td>
<td>Jones &amp; Jones 2002; Maehama et al. 2000</td>
</tr>
<tr>
<td>Diazoxide (Hyperstat)</td>
<td>Expert opinion</td>
<td>Erickson 1980</td>
</tr>
<tr>
<td>Phenazopyridine</td>
<td>Case report</td>
<td>Paola et al. 2003</td>
</tr>
</tbody>
</table>
Drug Name | Evidence | Author  
---|---|---
Intrathecal Baclofen | Case report | Kofler et al. 2009

7.0 Summary

There is level 4 evidence (from 5 pre-post studies) (Dykstra et al. 1988; Schurch et al. 2000; Chen et al. 2008; Kuo 2008; Chen & Kuo 2012) that Botulinum toxin injections into the detrusor muscle or external urethral sphincter seem to be a safe and valuable therapeutic option in SCI patients who perform clean intermittent self-catheterization and have incontinence resistant to anticholinergic medications.

There is level 4 evidence (from 1 pre-post study) (Igawa et al. 2003) that intravesical capsaicin is effective for reducing episodes of AD in SCI.

There is level 1 evidence (from 2 RCTs) (Kim et al. 2003; Giannantoni et al. 2002) that intravesical resiniferatoxin is effective for reducing episodes of AD in patients with SCI.

There is level 1 evidence (from 1 RCT) (Giannantoni et al. 2002) that intravesical resiniferatoxin is more effective than intravesical capsaicin.

There is level 5 evidence that anticholinergics (from 1 observational study) (Giannantoni et al. 1998) are not associated with reduced incidence of AD episodes.

There is level 4 evidence (from one pre-post study and one case series study) (Hohenfellner et al. 2001; Kutzenberger 2007) that sacral deafferentation may be effective in preventing AD.

There is level 4 evidence (based on four pre-post/case series studies) (Barton et al. 1986; Sidi et al. 1990; Perkash 2007; Ke & Kuo, 2010) that urinary bladder surgical augmentations may result in a decrease of intravesical and urethral pressure and therefore diminish or resolve episodes of AD.

There is level 4 evidence (based on 2 case series) (van der Merwe et al. 2012; Seoane-Rodriguez et al. 2007) that an intraurethral stent decreases incidence of AD and may be an effective means for the long-term management of detrusor-sphincter dysynergia for SCI patients, including those who have previously undergone sphincterotomy.

There is level 1 evidence (from 1 RCT) (Cosman & Vu 2005) that lidocaine anal block significantly limits the AD response in susceptible patients undergoing anorectal procedures.

There is level 1 evidence (from 1 RCT) (Cosman et al. 2002) that topical lidocaine does not limit or prevent AD in susceptible patients during anorectal procedures.

There is level 1 evidence (from 1 RCT) (Furusawa et al. 2008) that topical lidocaine may help to prevent AD during gentle bowel stimulation.

There is level 4 evidence that women with SCI may give birth vaginally. With vaginal delivery or when Caesarean delivery or instrumental delivery is indicated, adequate anesthesia (spinal or epidural if possible) is needed to reduce the episode of AD associated with birth.

There is level 4 and 5 evidence (from 2 case series and 2 observational studies) (Cross et al. 1992; Hughes et al. 1991; Cross et al. 1991; Showronski and Hartman 2008) that epidural anesthesia is preferred and effective for most patients with AD during labor and delivery.
There is level 5 evidence (from 2 observational studies) (Lambert et al. 1982; Eltorai et al. 1997) that indicate that patients at risk for autonomic dysreflexia are protected from developing intraoperative hypertension by either general or spinal anesthesia.

There is level 1 evidence (from one RCT) (Matthews et al. 1997) supporting no effect of topical anesthetic for the prevention of AD during FES.

There is level 4 evidence (Coggrave et al. 2012) that AD associated with bowel management decreases following stoma surgery.

There is level 4 evidence from one prospective study (Chen et al. 2012) that earlier surgical decompression after acute SCI results in decreased AD incidence as compared to delayed surgical compression.

There is level 2 evidence (from 2 prospective controlled trials) (Steinberger et al. 1990; Lindan et al. 1985) that Nifedipine may be useful to prevent dangerous blood pressure reactions, e.g. during cystoscopy and other diagnostic or therapeutic procedures in SCI injured patients with AD.

There is level 5 evidence (from clinical consensus) (Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure 1997), that serious adverse effects from Nifedipine may occur and these have been reported in other populations.

There is level 5 evidence (clinical consensus) (Consortium for Spinal Cord Medicine 2001; Braddom & Rocco 1991), but no clinical studies which support the use of nitrates in the acute management of AD in SCI.

There is level 4 evidence (from one pre-post study) (Esmail et al. 2002) for the use of captopril in the acute management of AD in SCI.

There is level 4 evidence (from 3 pre-post studies) (Vaidyanathan et al. 1998; Swierzewski et al. 1994; Chancellor et al. 1994) that regular use of Terazosin may have positive effects on incontinence and AD.

There is level 1 evidence (from one RCT) (Krum et al. 1992), that Prazosin is superior to placebo in the prophylactic management of AD.

There is level 4 evidence (from one pre-post study and one case series study) for use of Phenoxybenzamine in the management of AD; however, the results are conflicting with no effects seen in one study (Lindan et al. 1985) and positive effects in another (McGuire et al. 1976).

There is level 2 evidence from a very small prospective controlled study (Frankel & Mathias 1980) which used subjects as their own controls which showed that the level of BP recorded during electrical ejaculation was substantially reduced with Prostaglandin E2.

There is level 2 evidence (from 1 RCT) (Sheel et al. 1995) that sildenafil citrate had no effect on changes in BP during episodes of AD initiated by penile vibrostimulation in men with SCI.
8.0 References


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