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SPINAL CORD INJURY REHABILITATION EVIDENCE

Autonomic Dysreflexia and Other Autonomic Dysfunctions Following Spinal Cord Injury

Andrei Krassioukov, MD, PhD FRCPC
Jeff Blackmer, MD, FRCPC
Robert W Teasell, MD, FRCPC
Janice J Eng, PhD, BSc (PT/OT)

icord

Rick Hansen Institute
Institut Rick Hansen

Ontario Neurotrauma Foundation
Fondation ontarienne de neurotraumatologie

LAWSON HEALTH RESEARCH INSTITUTE
Aging, Rehabilitation & Geriatric Care

Western

UBC

G.F. Strong Rehab Centre
A part of the Vancouver Coastal Health Authority

St Joseph's Health Care London

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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Krassioukov A, Blackmer J, Teasell RW, Eng JJ (2014). Autonomic Dysreflexia Following Spinal Cord Injury. In Eng JJ, Teasell RW, Miller WC, Wolfe DL, Townson AF, Hsieh JTC, Connolly SJ, Noonan VK, Loh E, McIntyre A, Querée M, editors. Spinal Cord Injury Rehabilitation Evidence. Version 6.0. Vancouver: p 1- 50.

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Abbreviations

ACE	angiotensin I-converting enzyme
AD	autonomic dysreflexia
AIS	ASIA Impairment Scale
AUA	American Urological Association
BND	bladder neck disorder
BoNT-A	botulinum toxin A
BP	blood pressure
DBP	diastolic blood pressure
DESD	detrusor external sphincter dyssynergia
DVT	deep vein thrombus
ECG	electrocardiogram
FES	functional electrical stimulation
HR	heart rate
IEMG	integrated electromyography
IIQ-7	Incontinence Impact Questionnaire
IU	international unit (measurement unit of drugs)
IV	intravenous
MAP	mean arterial pressure
MCC	mean cystometric capacity
M/F	male/female
NBD	neurogenic bowel disorder
Para	paraplegic
PDE5	phosphodiesterase type 5
QoL	quality of life
RCT	randomized controlled trial
RTX	resiniferatoxin
SBP	systolic blood pressure
SCI	spinal cord injury
Tetra	tetraplegic
TURS	transurethral sphincterotomy
UDI-6	Urogenital Distress Inventory
UUT	upper urinary tract
UTI	urinary tract infection

Autonomic Dysreflexia and Other Autonomic Dysfunctions Following Spinal Cord Injury

1.0 Chapter Summary

What is autonomic dysreflexia?

Autonomic dysreflexia (AD) is a potentially life-threatening condition that can affect people who have had a spinal cord injury *at the level of T6 or above* (sometimes as low as T8, though rare – nerves from T6 control a large group of blood vessels that supply the lower body and many of the organs of the abdomen, such as the stomach and intestines; generally speaking, the higher the level of injury, the more likely it is that the circulatory system will be affected) (Krassioukov et al. 2003; Curt et al. 1997; Mathias & Frankel 1988). People with complete injuries are more often affected than people with incomplete injuries.

AD is a medical emergency that requires an immediate response. It occurs more often in the long term phase of SCI, but can happen in the first few months after injury as well. Episodes of autonomic dysreflexia are usually brief in duration and in most cases have an identifiable trigger that causes the episode (Teasell et al. 2000; Karlsson 1999; Mathias & Frankel 1988; Elliott & Krassioukov 2006).

What are the signs and symptoms of autonomic dysreflexia?

The main sign of autonomic dysreflexia is a sudden rise in blood pressure. An increase of 20 to 30 mmHg above your patient's normal *systolic blood pressure* is considered to indicate autonomic dysreflexia. Since the normal blood pressure of a person with a spinal cord injury can often be 15 to 20 mmHg lower than a person without a spinal cord injury, blood pressure can be in the range of 'normal' or 'slightly elevated' and still indicate an episode of AD.

Signs and symptoms of autonomic dysreflexia:

- Sudden rise in blood pressure of 20 to 30 mmHg above the person's normal *systolic blood pressure* (main symptom)
- Change in heart rate – usually a slow heart rate which can sometimes become rapid or irregular
- Pounding or throbbing headache
- Profuse sweating, flushing or blotching of the skin above the level of injury
- Goosebumps or hair standing on end above the level of injury
- Dry and pale skin below the level of injury
- Increased number and severity of muscle spasms
- Metallic taste in the mouth
- Feeling anxious or a feeling of impending doom
- Nasal congestion
- Blurred vision
- Seeing spots
- Nausea

- Difficulty breathing or a feeling of chest tightness

This rise in blood pressure is usually accompanied by other symptoms. These can range from not feeling anything or having some mild discomfort and a headache to a life-threatening emergency where symptoms can be severe. Symptoms can range from not feeling anything or having some mild discomfort and a headache to a life threatening emergency where symptoms can be severe. It is important for patients and clinicians to be able to recognize the symptoms of AD so you can act accordingly. Clinicians should also be aware that in some individuals with SCI, AD could occur without any symptoms and this condition known as a silent or asymptomatic AD (Ekland et al. 2008; Linsenmeyer et al. 1996).
While autonomic dysreflexia happens most often in the long term stage after injury, it can happen on occasion in the immediate post-injury period.

Why does autonomic dysreflexia happen?

Autonomic dysreflexia is the result of overactivity of the sympathetic nervous system in response to a strong sensory stimulus below the level of injury. This stimulus is often something that is noxious or irritating, such as a wound or tight clothing, but can also be a normal function of the body, such as an overly full bladder or bowel. In response to this stimulus, the sympathetic nervous system signals the arteries to constrict, which increases blood pressure. This increase in blood pressure is followed by a slowing of the heart rate which can then sometimes become irregular. Because of the damage to the spinal cord, the body can't effectively control the blood pressure and restore it to normal, resulting in autonomic dysreflexia. The most common trigger is irritation of the bladder or bowel.

Triggers of autonomic dysreflexia

Bladder issues
- Urinary tract infection
- Urinary retention
- Blocked catheter
- Overfilled collection bag

Skin issues
- Pressure ulcers
- Extreme heat or cold
- Pressure or pinching of the skin
- Ingrown toenails
- Burns
- Tight clothing
- Any direct irritant below the level of the injury

Other causes
- Heterotopic ossification
- Acute abdominal conditions (such as ulcers)
- Fractures

Bowel issues
- Distention or irritation of the bowel
- Constipation or impaction of the bowel
- Hemorrhoids
- Infection or irritation of the bowel

Sexual activity and reproductive processes
- Overstimulation
- Reproductive activity
- Menstrual cramping
- Labor and delivery

What to do if your patient has autonomic dysreflexia

1. Move patient into an upright

What should I do if my patient has an episode of Autonomic Dysreflexia?

Autonomic Dysreflexia is a medical emergency and requires immediate treatment. The most effective treatment strategy is to identify the trigger of the episode and reduce the stimulation that is causing it. The goal of intervention is to alleviate symptoms and avoid the complications associated with uncontrolled hypertension (Vallès et al. 2005; Eltorai et al. 1992; Pine et al. 1991; Yarkony et al. 1986).
If the conservative treatments for autonomic dysreflexia are not effective in reducing blood pressure and it remains at or above 150 mmHg, drug treatments are used. This involves the use of fast-acting anti-hypertensive drugs to rapidly lower the elevated blood pressure.

sitting position
2. Check blood pressure, and re-check every 5 minutes
3. Loosen tight clothing
4. Search for and eliminate the cause of the incident where one can be identified
    a. Check bladder
    b. Check bowel
    c. Check skin
5. Seek medical attention if there is no reduction in blood pressure after following these steps

Source: Consortium for Spinal Cord Medicine 2001).

Which prevention methods are effective?

Preventing an AD episode is far more effective than treating one (Braddom & Rocco 1991). Researchers have done studies on a number of different treatments to see which ones are helpful in preventing incidents of autonomic dysreflexia (Courtois et al. 2012; Krassioukov et al. 2009).

Capsaicin: Studies have shown that administering the chemical compound Capsaicin, and its more concentrated cousin Resiniferatoxin, into the bladder by a catheter, can decrease the number of episodes of AD during bladder procedures (Igawa et al. 2003; Kim et al. 2003; Giannantoni et al 2002).

Surgical bladder augmentation: Some early evidence suggests that surgery to augment the bladder may also reduce or resolve episodes of AD (Ke & Kuo 2010; Perkash 2007; Sidi et al. 1990; Barton et al. 1986).

Sacral denervation: Sacral deafferentation surgery may reduce bladder-related episodes of AD (Hohenfellner et al. 2001; Kutzenberger 2007).

Botulinum toxin: One study has demonstrated that injections of Botulinum toxin into the muscles of the bladder is effective in reducing episodes of AD (Fougere, Currie, Nigro, Stothers, Rapoport, and Krassioukov, 2016), which is supported by previous findings (Chen & Kuo 2012; Chen et al. 2008; Kuo 2008; Schurch et al. 2000; Dykstra et al 1988).

Anticholinergic medications: The use of anticholinergic medications does not appear to be effective in preventing AD during bladder procedures (Giannantoni et al. 1998).

Lidocaine: A lidocaine anal block has been found to limit the AD response in patients undergoing anorectal procedures. Topical lidocaine may prevent AD during digital bowel stimulation, but not during anorectal procedures (Furusawa et al. 2009; Cosman & Vu 2005; Cosman et al. 2002)**.**

Anesthesia for use during pregnancy and labour: Studies have found that the use of adequate anesthesia (spinal or epidural if possible) is needed with vaginal, Caesarean, or instrumental delivery to prevent AD during labour. Epidural anesthesia is preferred and effective for most

women with SCI (Skowronski & Hartman 2008; Cross et al. 1992; Cross et al. 1991; Hughes et al. 1991).

Anesthesia for use during general surgery: Anesthesia should be used during surgery for people with SCI despite the apparent lack of sensation, in order to prevent AD. Anesthesiologists and surgeons dealing with patients with SCI need to be able to recognize, prevent and manage it (Eltorai et al. 1997; Lambert et al. 1982).

Topical anesthesia during functional electrical stimulation (FES) treatment: Studies have found that the application of topical anesthesia is not effective in preventing AD during FES treatment. More research is required to understand how to prevent AD during FES (Matthews et al. 1997).

Stoma surgery: There is preliminary evidence that stoma surgery may reduce the number of incidents of autonomic dysreflexia, if other treatments have failed to improve management of neurogenic bowel (Coggrave et al. 2012).

Where can I find more information?

For more information please click through the rest of the Autonomic Dysreflexia chapter (https://scireproject.com/evidence/rehabilitation-evidence/autonomic-dysreflexia-re/) and consult a Doctor who specializes in SCI and/or Cardiovascular issues.

2.0 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 and Frankel, 1988;Mathias and Frankel, 2002;Teasell, Arnold, Krassioukov, and Delaney, 2000). 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, Arnold, Krassioukov, and Delaney, 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, Campagnolo, and Chou, 1996), mild discomfort and headache to a life threatening emergency when systolic blood pressure can reach 300mmHg (Mathias and 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 (Eltorai, Kim, Vulpe, Kasravi, and Ho, 1992;Pine, Miller, and Alonso, 1991;Valles, Benito, Portell, and Vidal, 2005;Yarkony, Katz, and Wu, 1986). 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 (Curt, Nitsche, Rodic, Schurch, and Dietz, 1997; Krassioukov, Furlan, and Fehlings, 2003; Mathias and Frankel, 1992). 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, Nitsche, Rodic, Schurch, and Dietz, 1997). AD is three times more prevalent in tetraplegics with a complete injury, in comparison to those with an incomplete injury (Curt, Nitsche, Rodic, Schurch, and Dietz, 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 (Krassioukov, Furlan, and Fehlings, 2003; Silver, 2000).

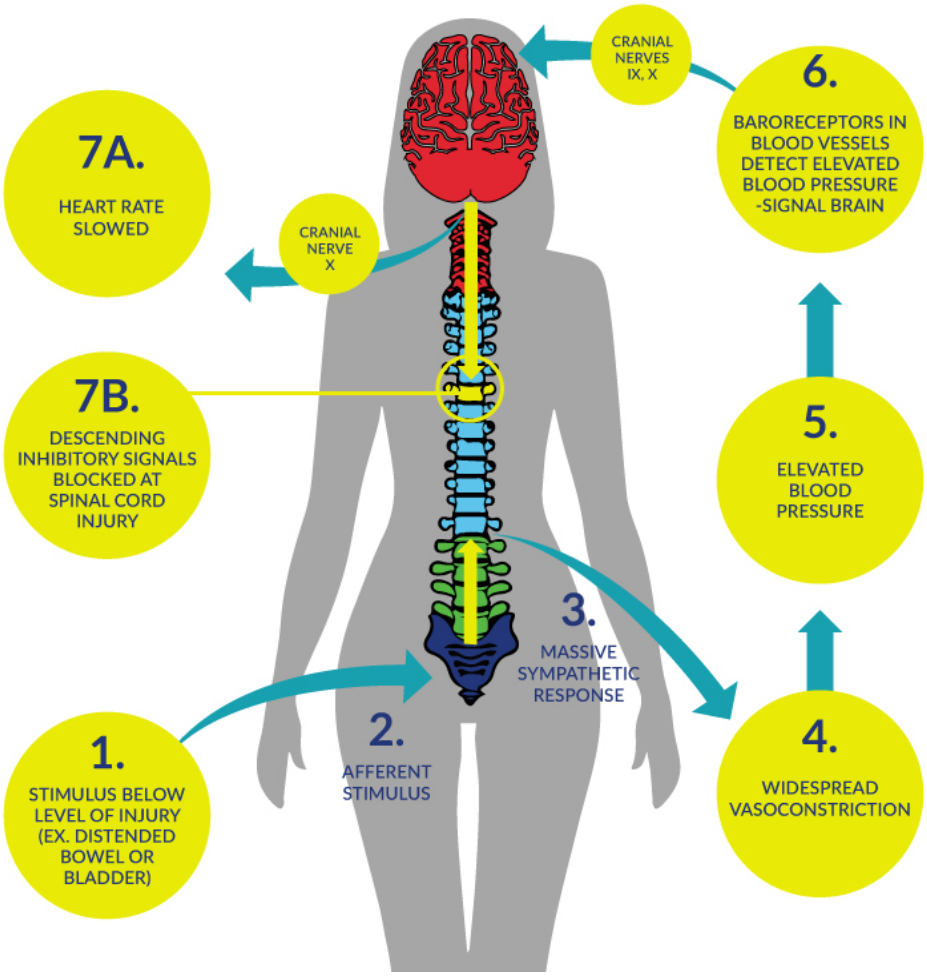


Figure 1 – Pathophysiology of Autonomic Dysreflexia

3.0 Pathophysiology of AD

AD is most commonly triggered by urinary bladder or colon irritation. However, many other causes have been reported in the literature (Mathias and Frankel, 2002; Teasell, Arnold, Krassioukov, and Delaney, 2000). AD is caused by massive sympathetic discharge triggered by either noxious or non-noxious stimuli below the level of the SCI (Krassioukov and Claydon, 2005). 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 and Krassioukov, 2005).

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 (Krassioukov, 2005;Mathias and Frankel, 1988;Mathias and Frankel, 2002;Teasell, Arnold, Krassioukov, and Delaney, 2000). 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, Fehlings, Shannon, Norenberg, and Krassioukov, 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 (Arnold, Feng, Delaney, and Teasell, 1995;Karlsson, 1999;Krassioukov, Bunge, Puckett, and Bygrave, 1999;Krassioukov, Johns, and Schramm, 2002;Krassioukov and Weaver, 1995;Krassioukov and Weaver, 1996;Osborn, Taylor, and Schramm, 1990).

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

3.1 How to Assess - Autonomic Assessment Form

The complexity of the autonomic nervous system and its involvement in almost every system in the body makes selecting appropriate autonomic function tests for individuals with SCI difficult (Krassioukov et al. 2007). It is not clear how many practitioners in SCI care have experience with testing in this area, even if the operational definitions of autonomic dysfunction are in place (Krassioukov et al. 2007). Inattention to autonomic function post-SCI might significantly risk a person's neurological function and quality of life (Krassioukov et al. 2007). During the last decade, the assessment of individuals with SCI has improved significantly, even though autonomic screening remains somewhat difficult to complete. Previous research has recommended that the assessment of autonomic functions be a part of clinical evaluation of individuals with SCI, in addition to already established motor and sensory assessment (Krassioukov et al. 2007).

The 'International Standards to Document Remaining Autonomic Function after Spinal Cord Injury' (ISAFSCI) was developed by a working group of the American Spinal Injury Association (ASIA) and International Spinal Cord Society (ISCoS) (Alexander et al. 2009; Krassioukov et al. 2012). The ISAFSCI is an assessment designed to determine which autonomic functions are intact, impaired or lost following SCI, and the Assessment form consists of 2 major sections – General Autonomic Function and Lower Urinary Tract, Bowel and Sexual Function (Krassioukov, 2012).

Appendix I

Autonomic Standards Assessment Form

Autonomic Diagnosis: (Supraconal ☐, Conal ☐, Cauda Equina ☐)

Patient Name: _____

General Autonomic Function

System/Organ	Findings	Abnormal conditions	Check mark
Autonomic control of the heart	Normal		
	Abnormal	Bradycardia	
		Tachycardia	
		Other dysrhythmias	
	Unknown		
	Unable to assess		
Autonomic control of blood pressure	Normal		
	Abnormal	Resting systolic blood pressure below 90 mmHg	
		Orthostatic hypotension	
		Autonomic dysreflexia	
	Unknown		
	Unable to assess		
Autonomic control of sweating	Normal		
	Abnormal	Hyperhydrosis above lesion	
		Hyperhydrosis below lesion	
		Hypohydrosis below lesion	
	Unknown		
	Unable to assess		
Temperature regulations	Normal		
	Abnormal	Hyperthermia	
		Hypothermia	
	Unknown		
	Unable to assess		
Autonomic and Somatic Control of Broncho-pulmonary System	Normal		
	Abnormal	Unable to voluntarily breathe requiring full ventilatory support	
		Impaired voluntary breathing requiring partial vent support	
		Voluntary respiration impaired does not require vent support	
	Unknown		
	Unable to assess		

Lower Urinary Tract, Bowel and Sexual Function

System/Organ		Score
Lower Urinary Tract		
Awareness of the need to empty the bladder		
Ability to prevent leakage (continence)		
Bladder emptying method (specify)_____		
Bowel		
Sensation of need for a bowel movement		
Ability to Prevent Stool Leakage (continence)		
Voluntary sphincter contraction		
Sexual Function		
Genital arousal (erection or lubrication)	Psychogenic	
	Reflex	
Orgasm		
Ejaculation (male only)		
Sensation of Menses (female only)		

2=Normal function, 1=Reduced or Altered Neurological Function
0=Complete loss of control, NT=Unable to assess due to preexisting or concomitant problems

Date of Injury_____ Date of Assessment_____

This form may be freely copied and reproduced but not modified.
This assessment should use the terminology found in the International SCI Data Sets (ASIA and ISCoS - http://www.iscos.org.uk)

Examiner _____

Figure 2 – Autonomic Standards Assessment Form – Available from: http://www.iscos.org.uk/sitefiles/PageFile_20_Autonomic%20Standards%20Assessment%20Form%20FINAL%202009.pdf

4.0 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

Authors; Country Date included in the review Total Sample Size Level of Evidence Type of Study Score	Methods Databases	Conclusions
Liu et al. 2015 Canada Reviewed published articles from 1956 to 2014 N=40 **Level of Evidence:** Methodological quality not assessed **Types of study:** Information not provided AMSTAR: 5	**Methods:** Literature search for English articles, including original articles, practice guidelines, case reports and literature reviews, pertaining to iatrogenic urological triggers of AD following SCI. Studies with no data on AD or changes in blood pressure during urological assessments were excluded. The keywords used during the search were population search terms that included 'paraplegia', 'tetraplegia', 'quadriplegia', 'spinal cord inj*', 'spinal cord dys*(function)', 'spinal cord dis*' and 'spinal cord lesion', as well as 'autonomic dysreflexia' or 'autonomic hyperreflexia'. **Databases:** PubMed	1. The included articles were divided into four groups according to the urological procedure: 1) urodynamics and cystometry (n = 21); 2) cystoscopy and transurethral litholapaxy (n = 12); 3) extracorporeal shock-wave lithotripsy (ESWL) (n = 6); and 4) other procedures (n = 2). 2. Incidence of AD ranged from 36.7%- 77.8% in urodynamics. AD symptomatic rate ranged from 50%-65%. 3. No relationship between AD and neurogenic detrusor overactivity or detrusor sphincter dyssynergia. 4. The majority of patients without anesthesia developed AD during cystoscopy, transurethral litholapaxy, and EWSL. 5. Nifedipine was shown to be most effective medication during urodynamics, cystoscopy and ESWL for relief of acute AD and for prevention of AD. 6. Flexible cystoscopy is accepted as an effective alternative to rigid endoscopy in minimizing occurrence of AD 7. Common types of anesthesia used for individuals with SCI include local, subarachnoid, epidural, and general anesthesia. 8. The effectiveness of different anesthesia methods is dependent on blocking nociceptive signals from the lower urinary tract (LUT) below the level of injury.
Krassioukov et al. 2009; Canada Reviewed published articles from 1950 to 2007 N=31 **Level of Evidence:** PEDro scale – RCTs, Modified Downs and Black – non-RCTs **Types of study:** 6 RCTs 11 pre-post 5 observational 5 case series 3 prospective controlled 1 case report AMSTAR: 5	**Methods:** 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. **Databases:** PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO	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.

Authors; Country Date included in the review Total Sample Size Level of Evidence Type of Study Score	Methods Databases	Conclusions
Courtois et al. 2012 Canada Reviewed published articles from 1948 to 2011 N=37 **Level of Evidence:** Methodological quality not assessed **Types of studies:** Information not provided AMSTAR: 2	**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 E_2, sildenafil, captopril, terazosin, doxazosin, phenoxybenzamine) 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. **Databases:** PubMed/MEDLINE	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.

Discussion

We found three 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. Liu et al. (2015) explored the latrogenic urological triggers of AD. AD has a high incidence rate in urodynamics and the majority of patients without anesthesia developed AD during cystoscopy, transurethral litholapaxy, and EWSL. Nifedipine was shown to be the most effective medication during urodynamics, cystoscopy and ESWL for relief of acute AD and for prevention of AD. 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.

5.0 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 (Blackmer, 2003;Mathias and Frankel, 2002;Teasell, Arnold, Krassioukov, and Delaney, 2000).

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 (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 (Mathias and Frankel, 2002;Teasell, Arnold, Krassioukov, and Delaney, 2000). 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 (1997). The goal of such an intervention is to alleviate symptoms and avoid the complications associated with uncontrolled hypertension (Eltorai, Kim, Vulpe, Kasravi, and Ho, 1992;Pine, Miller, and Alonso, 1991;Valles, Benito, Portell, and Vidal, 2005;Yarkony, Katz, and Wu, 1986).

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

6.0 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.

6.1 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.

Table 3: Prevention of AD during Bladder Procedures

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Xiong et al. 2015 China Case Series N=89	**Population:** 89 SCI cases with bladder stones undergoing cystolitholapaxy 64 males, 25 females Mean (SD) age in years = 35.98 (8.17) Injury level: 57 subjects above T6 **Treatment:** 48 with with spinal anesthesia, 26 with general anesthesia, 15 with local anesthesia **Outcome Measures:** Presence of AD, stone size and number, length of surgery	1. Of the 89 patients, 31 (34.83%) developed AD during the operation 2. Patients with AD had larger stones (4.58+/-1.26 cm vs. 3.75+/-1.15cm) and a higher number of stones (2.29+/-0.86 vs. 1.74+/-0.81) 3. 83.87% of patients with AD had lesion level at or above T6 vs. 41.38% in non AD group 4. Operation time was longer in AD group vs. non AD group (60.65+/-17.78 min vs. 49.31+/-14.31 min) 1. Incidence rate of AD was highest in patients with local anesthesia (18/20, 90%), followed by general anesthesia (12/27, 44.44%) and spinal anesthesia (1/40, 2.5%)

Discussion

One case series (n=89) (Xiong et al. 2015) revealed that individuals experiencing AD during cystolitholapaxy had larger bladder stones, a higher number of bladder stones, and longer operation time. Spinal anesthesia may be the most effective way to prevent incidence of AD in cystolitholapaxy procedures as only 2.5% of participants with spinal anesthesia experienced AD.

There is level 4 evidence (from one case series) (Xiong et al. 2015) that spinal anesthesia may be more effective at preventing incidence of AD during cystolitholapaxy compared to local or general anesthesia.

6.1.1 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 4: Botulinum Toxin and AD

Author Year; Country Score Research Design Sample Size	Methods	Outcome

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Fougere et al. 2016 Canada Pre-post N=17	**Population:** N=17 (12M, 5F) with chronic traumatic SCI at or above T6 and concomitant autonomic dysreflexia and neurogenic detrusor overactivity Mean (SD) age: 44 (10) Mean (SD) years post injury: 21 (11) AIS-A/B/C = 9/5/3 11 cervical, 6 thoracic **Treatment:** One cycle of Botox injection (200U in 20mL 0.9% saline, injected into 20 sites of detrusor muscle), 2wk after baseline measurements & 1mo before post-treatment measurements **Outcome Measures:** Urodynamic studies (UDS), 24h ambulatory BP monitoring (ABPM), AD Health-related QoL questionnaire, I-QOL questionnaire	1. Pre vs. post-botox during UDS (mean±SD): Significantly lower SBP (mmHg) at: First urge to preform CIC (112±17 vs. 114±14), at max volume infused (151±25 vs. 133±17), and at max SBP (153±25 vs. 134±16) Significantly lower ΔSBP* (mmHg) at: First urge to preform CIC (34±20 vs. 15±11), at max volume infused (40±24 vs. 18±12), and at max SBP (42±23 vs. 20±10) Significantly lower ΔHR (bpm) at: First urge to preform CIC (-8±11 vs. -6±10), at max volume infused (-17±12 vs. -9±14), and at max SBP (-16±13 vs. -8±14) 2. Pre vs. post-botox during bladder events (mean±SD, from 24h ABPM): Significantly reduced max SBP (157±21 vs. 139±21) & ΔSBP** during CIC 3. AD eliminated in 10 participants (ΔSBP <20mmHg), attenuated in 7 4. Significantly fewer participants reporting AD symptoms post-botox (15 to 9) 5. Significantly reduced frequency of AD during CIC post-treatment (67% to 25%) 6. Significant improvement in all subsections and in total scores of QoL measures *change in measure vs. supine baseline **change in measure vs. seated baseline CIC = clean intermittent catheterization
Chen & Kuo 2012; Taiwan Pre-post N=49 (with AD=34)	**Population:** 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. **Treatment:** Patients received two sets of 200 U BoNT-A injections into the detrusor at baseline and 6 months later. **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.	1. 15 patients did not have AD at baseline or after treatment. 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. 3. No significant differences in any urodynamic variables between patients with and without AD. 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. 5. No significant difference in the quality of life index between patients with and without AD at the end point.
Chen et al. 2008; Taiwan Pre-post	**Population:** 20 suprasacral SCI subjects with detrusor external sphincter dyssynergia (DESD); Mean age 37.9 (15.7); 17 male; 12	1. 4 patients who had AD symptoms before treatment reported decreased frequency and intensity of AD.

Author Year; Country Score Research Design Sample Size	Methods	Outcome
N=20 (with AD=4)	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. **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) uV), as well as static urethral pressure (from 139.4(40.5) to 104.8(30.5) cmH_2O) and maximal urethral pressure (from 107.5(69.1) to 80.2(35.7) cmH_2O). 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.
Kuo 2008; Taiwan Pre-post N=33 (with AD=6)	**Population:** 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 normal saline into eight sites of the urethral sphincter. **Outcome Measures:** video-urodynamic studies; Urogenital Distress Inventory short form (UDI-6); Incontinence Impact Questionnaire (IIQ-7) short form.	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) cmH_2O), 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). 3. IIQ-7 scores were significantly improved, but not the UDI-6 scores.
Schurch et al. 2000; Switzerland Pre-post N initial=31 N final=19	**Population:** 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. **Treatment:** Botulinum-A toxin was injected (200-300 units) into the detrusor muscle. **Outcome Measures:** voiding and detrusor pressure, diary of incontinence, AD symptoms at 6, 16, and 36-wks.	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.
Dykstra et al. 1988; USA Pre-post N=11 (with AD=7)	**Population:** Detrusor-sphincter dyssynergia **Treatment:** low dose botulinum A toxin at the neuromuscular junction. **Outcome Measures:** urethral pressure, symptoms of AD.	1. Urethral pressure profile decreased 27 cm H_20 (n=7). 2. Self-assessed improvement of AD symptoms in 5 of 7 AD patients. 3. Toxin effects lasted an average of 50 days.

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.

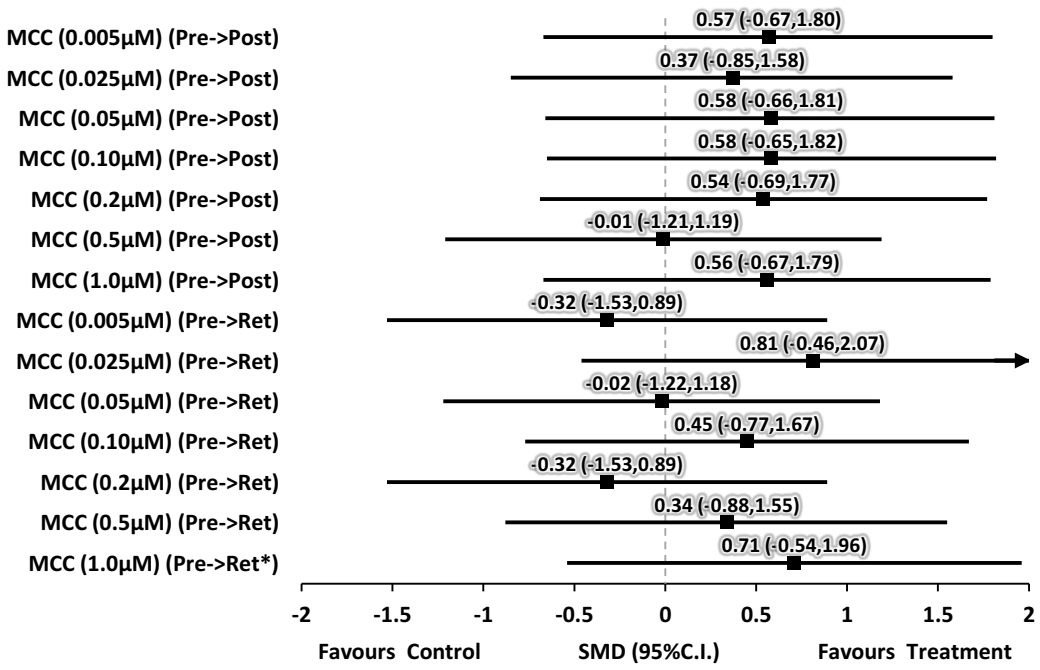
Botulinum toxin injections into the detrusor muscle or external urethral sphincter seem to be a safe and valuable therapeutic option in SCI patients who perform clean intermittent self-catheterization and have incontinence resistant to anticholinergic medications. Its use in the prevention of AD is less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

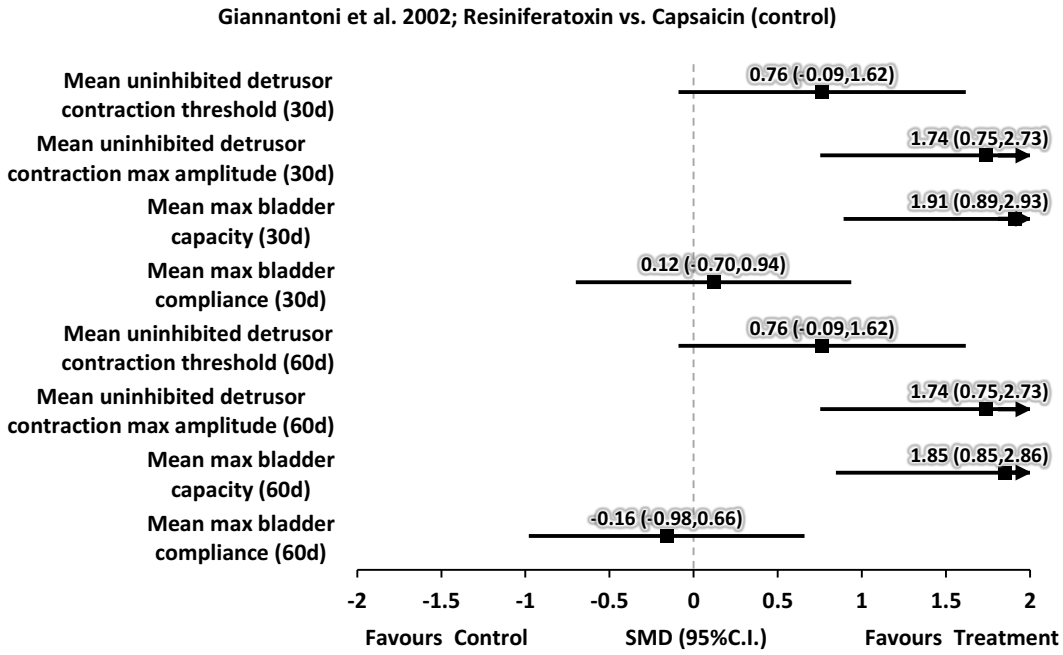
6.1.2 Intravesical Capsaicin

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 5: Capsaicin

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Kim et al. 2003; USA PEDro=9 RCT N=36	**Population:** 22 males, 14 females, neurologically impaired patients (20 SCI, 7 multiple sclerosis, and 9 others) with urodynamically verified detrusor hyperreflexia. **Treatment:** Randomized double blind, placebo-controlled trial. Intravesical instillation of Resiniferatoxin (RTX) 0.005, 0.025, 0.05, 0.10, 0.2, 0.5, or 1.0 microM of RTX (n=4 each group) or placebo (n=8). **Outcome Measures:** incontinence episodes, bladder capacity.	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.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data	

Author Year; Country Score Research Design Sample Size	Methods	Outcome
	 ***Retention data for 1.0µM from 6 week post-baseline (12 week post-baseline otherwise)**	
Giannantoni et al. 2002; Italy PEDro=6 RCT N=23	**Population:** 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. **Outcome Measures:** Urodynamics, frequency of daily catheterizations, incontinence episodes and side effects.	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.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- to post-intervention data	

Author Year; Country Score Research Design Sample Size	Methods	Outcome
	 **Effet size calculated for 1) pre-intervention to 30 days (30d) post-intervention and 2) pre-intervention to 60 days (60d) post-intervention**	
Igawa et al. 2003; Japan Pre-post N=7	**Population:** 5 subjects with cervical injuries and 2 subjects with thoracic injuries. **Treatment:** bladder instillation with capsaicin solution under general anesthesia. **Outcome Measures:** blood pressure, heart rate, serum catecholamines, blood ethanol concentration.	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 > 3 months.

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 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.

6.1.3 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 6: Anticholinergics

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Giannantoni et al. 1998; Italy Observational N=48	**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.	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.

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.

6.1.4 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 7: Sacral Denervation

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Kutzenberger 2007; Germany Case series Initial N=464 Final N=440	**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.	1. Autonomic dysreflexia disappeared in all cases with the exception of two. In these individuals, blood pressure was maintained at less dangerous levels.
Hohenfellner et al. 2001; Germany Pre-post N=9 (with AD=5)	**Population:** detrusor hyperreflexia. **Treatment:** sacral bladder denervation. **Outcome Measures:** bladder capacity, blood pressure, symptomatic AD.	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.
Schurch et al. 1998; Switzerland Case series N=10	**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.	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.

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.

Sacral deafferentation may reduce AD during urodynamic investigations.

6.1.5 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 8: Bladder and Urethral Sphincter Surgery

Author Year; Country Score Research Design Sample Size	Methods	Outcome
van der Merwe et al. 2012; South Africa Case series N=28	**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.	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.
Ke & Kuo 2010; Taiwan Case series N=22	**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.	1. Spontaneous voiding resumed in 19 patients, persistent urinary retention in 3 patients. 2. Urodynamic parameters: For patients with a Pdet > 15cmH2O at baseline, after surgery: Pdet and PVR decreased, Qmax increased 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.
Perkash 2007; USA Case series N=46	**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 dysreflexia during cystometrogram (measures the contractile force of the bladder when voiding), blood pressure.	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. 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.
Seoane-Rodriguez et al. 2007; Spain Case series N=47	**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	1. Decrease in symptomatic UTI by 25%. 2. Decrease in post void residual urine volume by an average of 224.3 cm^3. 3. Episodes of dysreflexia decreased from 35.1% to 16.2%. 4. Complications in the UUT decreased from

Author Year; Country Score Research Design Sample Size	Methods	Outcome
	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.	46.8 to 23.4%. 5. Urodynamic study showed an average reduction of 44.4 cm^3 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.
Sidi et al. 1990; USA Pre-post N=12	**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.
Barton et al. 1986; USA Case series N=16	**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.

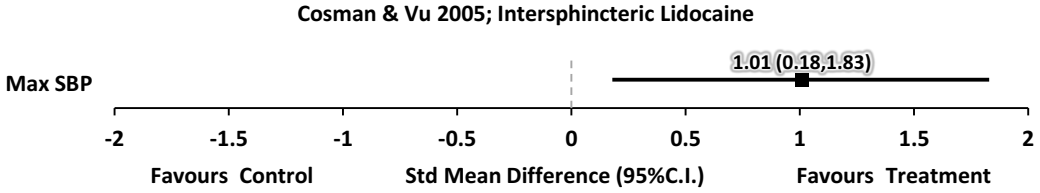
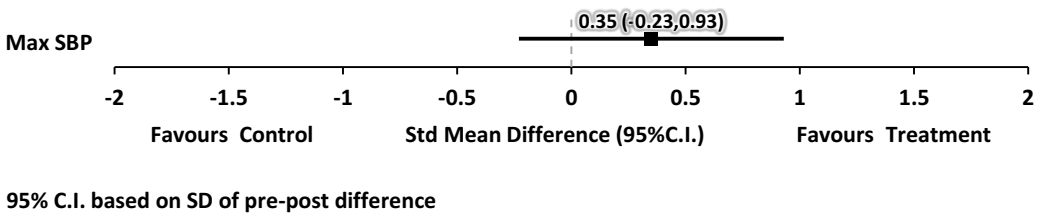
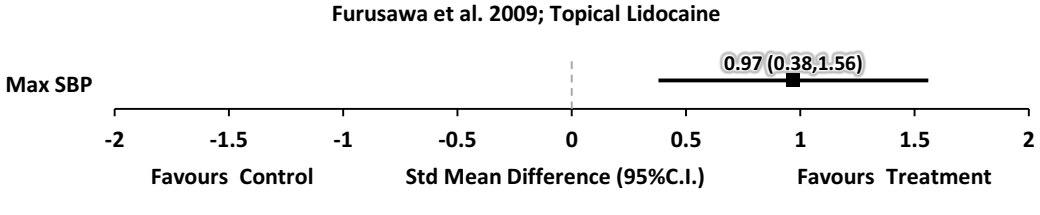
Urinary bladder surgical augmentations may diminish or resolve episodes of AD.

6.2 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 9: Prevention of AD during Anorectal Procedures

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Cosman & Vu 2005; USA PEDro=11 RCT N=25	**Population:** Al l subjects with complete SCI; age 46-49 years; 15-25 years post-injury; level of injury: C4-T1 **Treatment:** intersphincteric anal block with either: a) 300 mg 1% lidocaine or b) normal saline (placebo) before sigmoidoscopy or anoscopic hemorrhoid ligation procedure. **Outcome Measures:** blood pressure.	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.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data	

Author Year; Country Score Research Design Sample Size	Methods	Outcome
	 95% C.I. based on SD of pre-post difference	
Cosman et al. 2002; USA PEDro=9 RCT N=45	**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).
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data  95% C.I. based on SD of pre-post difference	
Furusawa et al. 2009; Japan PEDro=8 RCT N=25	**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.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data  95% C.I. based on SD of pre-post difference	

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 & Vu 2005). 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.

6.3 Prevention of AD during Pregnancy and Labour

In North America, women represent a third of the SCI population (Ackery, Tator, and Krassioukov, 2004). Approximately 3,000 American women of childbearing age are affected by SCI (Cross, Meythaler, Tuel, and Cross, 1992). The ability of women to have children is not usually affected by SCI once their menstrual cycle resumes (Jackson and Wadley, 1999). There are increasing numbers of women with SCI who have healthy babies (Cross, Meythaler, Tuel, and Cross, 1992). However, during labour and delivery, susceptible women with SCI are at high risk of developing uncontrolled AD (Sipski, 1991;Sipski and 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 10: Prevention of AD during Pregnancy and Labour

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Sharpe et al. 2015 USA Case Series N=8	**Population:** Eight patients with SCI undergoing nine deliveries Median time from injury to time of delivery = 13 years (range 2–19 years) ASIA A=6, ASIA B=1, ASIA D=1	1. Only patients with previous AD episodes presented AD symptoms during peripartum period. 2. Of the 4 patients with pre-pregnancy AD, 3 had AD symptoms peripartum.

Author Year; Country Score Research Design Sample Size	Methods	Outcome
	Pre-pregnancy AD: n=4 **Treatment:** 5 with epidural anesthesia, 2 with spinal anesthesia, 2 with general anesthesia **Outcome Measures:** Outcomes of pregnancies, presence of AD	3. One experienced AD during epidural placement, one during the second stage of labor, and all 3 experienced AD in the postpartum period. 4. No blood pressure measurements were recorded during these episodes, suggesting staff may not be aware of risk of AD in SCI patients
Skowronski & Hartman 2008; Australia Case series N=5	**Population:** 5 females with tetraplegia who gave birth a total of 7 times (two subjects gave birth twice). **Treatment:** N/A **Outcome Measures:** Complication, management, and outcomes of pregnancy; hospital records.	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).
Cross et al. 1992; USA Case series N=22	**Population:** 22 women with SCI, 11 with cervical and 11 with thoracic injuries; 10 with incomplete and 12 with complete injuries. **Treatment:** epidural anesthesia. **Outcome Measures:** presence of autonomic hyperreflexia, type of anesthesia, type of delivery, complications.	1. AD was experienced in 9/16 > 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.
Cross et al. 1991; USA Observational N=16	**Population:** 7 subjects with cervical and 9 with thoracic injuries. **Treatment:** questionnaire (in person or telephone) and hospital records review. **Outcome Measures**: outcomes of pregnancies.	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.
Hughes et al. 1991; UK Observational N=15	**Population:** 17 pregnancies in 15 women with SCI, level of injury: T4-L3. **Treatment:** management and outcome of pregnancies in women with SCI. **Outcome Measures**: antenatal care and problems, labour diagnosis and outcome.	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.
Ravindran et al. 1981; USA Case report N=1	**Population:** 19 yr-old female with C5 complete tetraplegia admitted to the obstetrical intensive care unit for intra-amniotic prostaglandin F2-alpha injection for uterine evacuation of a dead fetus of 20 wks gestation. **Treatment:** Sodium nitroprusside (100 mg/min to 700 mg/min). **Outcome measures:** BP and AD symptoms.	1. 100 mg/min of sodium nitroprusside decreased SBP from 170 mmHg to 120 mmHg caused by vaginal speculum introduction. 2. Prostaglandin induced uterine contraction further elevated BP to 200/70 mmHg; headache and sweating. 3. Administration of 700 mg/min of sodium nitroprusside decreased SBP and alleviated AD.

Author Year; Country Score Research Design Sample Size	Methods	Outcome
		4. Following cessation of uterine contraction, the patient developed hypotension (70/30 mmHg) requiring vasopressor therapy. 5. Sodium nitropruside was stopped and epidural analgesia was initiated for further management of AD.

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 six studies (n=67) (Cross et al. 1992; Hughes et al. 1991; Cross et al. 1991; Ravindran et al. 1981; Skowronski & Hartman 2008; Sharpe et al. 2015) 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 3 case series and 2 observational studies) (Cross et al. 1992; Hughes et al. 1991; Cross et al. 1991; Showronski and Hartman 2008; Sharpe et al. 2015) 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.

6.4 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 11: Prevention of AD during Surgery

Author Year; Country Score Research Design Sample Size	Methods	Outcome

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Eltorai et al. 1997; USA Observational N=591	**Population**: Level of injury: C1-T10, mean length of injury: 22.3 yrs. **Treatment:** retrospective review of anesthetic methods during surgery. **Outcome Measures:** blood pressure.	1. AD occurred most commonly during the start of anesthesia (induction) with the greatest frequency when no anesthesia was provided. 2. 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.
Lambert et al. 1982; USA Observational N=50	**Population:** Subjects had injuries that were above T6, and complete; mean of 6.5 years post-injury. **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). **Outcome Measures:** blood pressure.	1. Intraoperative hypertension occurred more significantly with topical or no anesthesia (15/19) compared to general anesthesia (3/13) or spinal anesthesia (3/46). 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.

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.

6.5 Prevention of AD during FES Exercise

Functional electrical stimulation (FES) is a widely-used modality in the rehabilitation of individuals with SCI (Sampson, Burnham, and Andrews, 2000;Wood, Dunkerley, and Tromans, 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, Laskin, Olenik, Burnham, Steadward, Cumming, and Wheeler, 1993;Matthews, Wheeler, Burnham, Malone, and Steadward, 1997).

Table 12: Prevention of AD during FES Exercise

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

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, Wheeler, Burnham, Malone, and Steadward, 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.

6.6 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 13: Prevention of AD with Stoma

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Coggrave et al. 2012; UK Cross-sectional N=92	**Population:** 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. **Treatment:** Retrospective analysis of a self-report postal survey of individuals with SCI who had a stoma.	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).

Author Year; Country Score Research Design Sample Size	Methods	Outcome
	Outcome Measures: Tennessee Self-Concept Scale; Satisfaction with Life Scale; Hospital Anxiety and Depression Scale; rating scales for satisfaction, ability to live with bowel dysfunction and how much bowel care restricts life.	

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.

6.7 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 14: Prevention of AD in Acute Care

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Chen et al. 2012; China Pre-Post (Multiple Groups) N=295	**Population:** 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). **Treatment:** 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. **Outcome Measures:** ASIA motor index total score; ASIA Impairment Scale (AIS); Motor and sensory scores of injured level; medical complications.	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%)

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.

7.0 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).

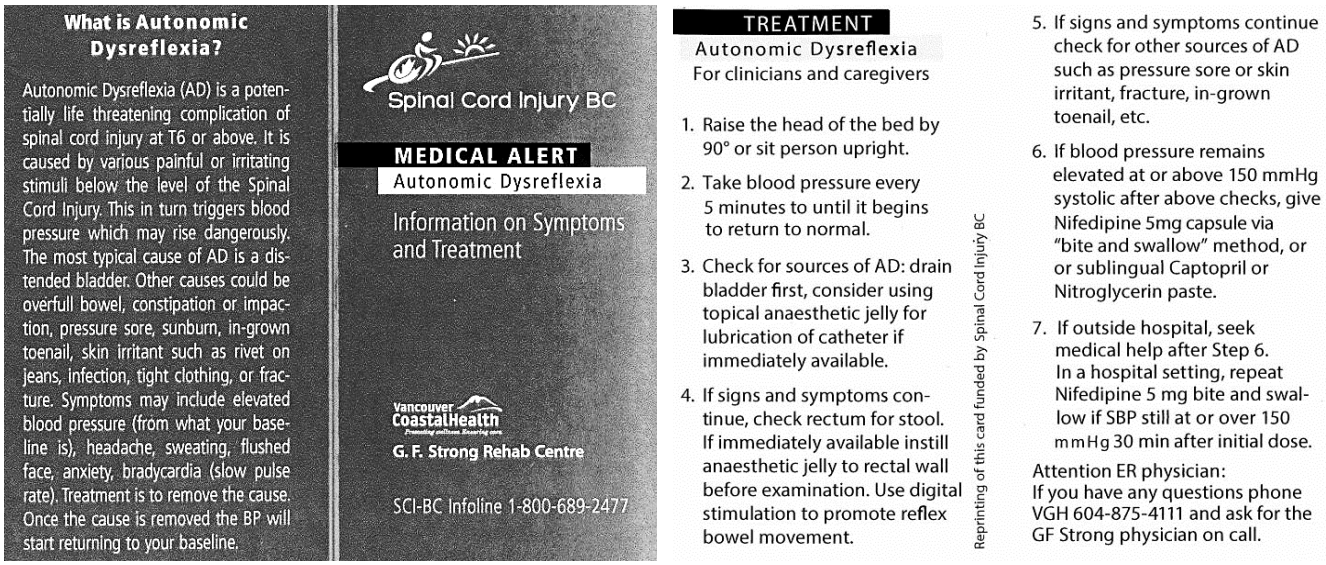


Figure 3 - Autonomic Dysreflexia Symptom and Treatment care from SCI-BC (https://sci-bc.ca/)

7.1 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).

7.2 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 2001). 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, sildanefil) 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.

7.2.1 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 15: Nifedipine (Adalat, Procardia)

Author Year; Country Score Research Design Sample Size	Methods	Outcome

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Thyberg et al. 1994; Sweden Pre-post N=10	**Population:** 10 subjects with cervical or high thoracic SCI. **Treatment:** 10 mg nifedipine sublingually during cystometry. **Outcome Measures:** blood pressure and heart rate.	1. Patients demonstrated decreased maximum SBP and DBP after the administration of nifedipine. 2. Maximum SBP decreased from 147 mmHg to 118 mmHg. 3. The decrease in BP was due to a decrease in baseline pressure and BP response during cystometry.
Kabalin et al. 1993; USA Case series N=20	**Population:** 10 subjects with tetraplegia, 10 with paraplegia. **Treatment:** 10-30 mg nifedipine sublingually during Estracorporal shock wave lithotripsy (ESWL) for kidney stone treatment. **Outcome Measures:** electrocardiogram, blood pressure, pulse rate, peripheral oxygen saturation.	1. All but one SCI patient demonstrated AD during ESWL with maximal increase in systolic BP of 74 mmHg. 2. Nifedipine was administered sublingually and controlled BP elevation. 3. For severe, acute increases in BP, ESWL stimulation was momentarily discontinued until pharmacological control of the BP was achieved, after which treatment was continued.
Steinberger et al. 1990; USA Prospective controlled trial N=10	**Population:** All subjects with injury levels above T5; mean 9 years post-injury (range 3-21 years). **Treatment:** 10-30 mg nifedipine sublingually 15 min prior to electroejaculation or no nifedipine. **Outcome Measures:** blood pressure, voltage and current delivered during electroejaculation.	1. In 9/10 patients, blood pressures were markedly lower after nifedipine pretreatment. 2. Compared with no treatment, SBP during electroejaculation was lower with nifedipine pretreatment (168 mmHg vs. 196 mmHg). 3. In 9/10 patients, tolerance to electrical stimulation was ≥ post nifedipine pretreatment.
Dykstra et al. 1987; USA Pre-post N=7	**Population:** Subjects with **c**omplete, cervical injuries. **Treatment:** 10 mg nifedipine during cystosopy procedure. **Outcome measures:** blood pressure, presence of AD.	1. Nifedipine alleviated AD when given sublingually during cystoscopy and prevented autonomic hyperreflexia when given orally 30 minutes before cystoscopy. 2. No adverse drug effects were observed.
Lindan et al. 1985; USA Prospective controlled trial N=12	**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.

7.2.2 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.

7.2.3 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 16: Captopril

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Esmail et al. 2002; Canada Pre-post N=7	**Population:** 26 consecutive patients older than 15 years with SCI above T6. **Treatment:** administration of a) captopril 25mg sublingually if systolic blood 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	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. 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.

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

7.2.4 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 17: Terazosin

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Vaidyanathan et al. 1998; UK Pre-post N=24	**Population:** 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. **Treatment:** 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. **Outcome Measures:** drug-induced hypotension, adverse effects, AD symptoms.	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.
Chancellor et al. 1994; USA Pre-post N=21	**Population:** 21 subjects with complete SCI; injury level C3-T5. **Treatment:** Terazosin administration. **Outcome Measures**: blood pressure and autonomic dysreflexia frequency and severity scores	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. 4. SBP did not statistically change after 3 months of Terazosin.
Swierzewski et al. 1994; USA Pre-post N=12	**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.	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.

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

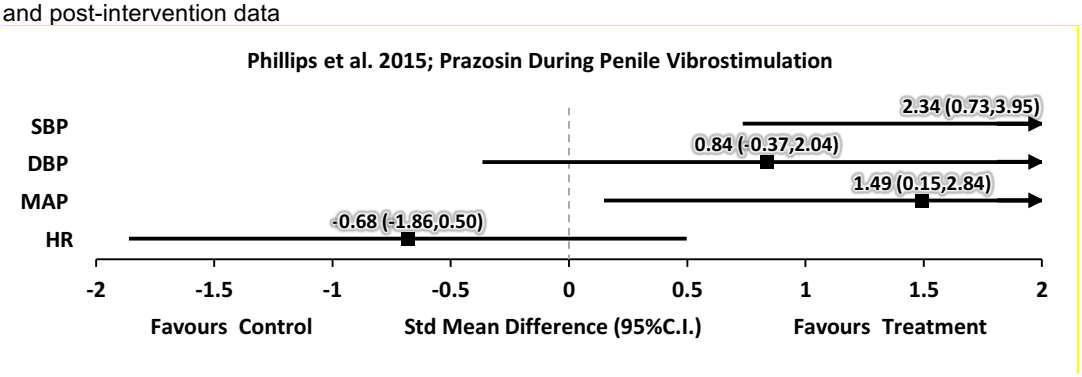
There is level 4 evidence (from 3 pre-post studies) (Vaidyanathan et al. 1998; Swierzewski et al. 1994; Chancellor et al. 1994) that regular use of Terazosin may have positive effects on both incontinence and AD.

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

7.2.5 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 18: Prazosin (Minipress)

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Phillips et al. 2015 Canada PEDro = 9 RCT N= 6	**Population**: N = 6 males with complete, chronic SCI above T6 Mean (SD) age: 36.7 (4.8) years Mean (SD) time since injury: 139 (47.3) months ASIA A=3; ASIA B=1; ASIA D=2 Cause of SCI: MVA=3; Athletics=2; Fall=1 **Treatment**: Subjects had 2 penile vibrostimulation (PVS) trials; one with prazosin, other with a placebo (sugar capsule) **Outcome Measures:** Cardiovascular parameters (HR and continuous beat-to-beat BP)	1. All patients experienced AD during PVS regardless of treatment: BP increased in all patients but HR did not change 2. On average, systolic BP was 44 mm Hg lower when prazosin was administered. 3. SBP increased an average of 140 +/- 19 mm Hg with placebo, and increased only 96 +/- 14 mm Hg with prazosin 4. Of the six participants, five had a mitigation of SBP increases when treated with prazosin compared to placebo (the remaining subject had no change in BP response) 5. Prazosin had no effect on resting BP
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data 	
Krum et al. 1992; Australia PEDro=9 RCT N=15	**Population:** Level of injury: T6 or above, at least 2 episodes of AD in last 7 days. **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.	1. Prazosin was well tolerated and did not significantly lower resting BP. Compared to baseline, the Prazosin group had fewer severe episodes of AD (reduced rise in BP, shorter symptom duration and less need for acute antihypertensive medication). 2. The severity of headache during individual AD episodes was also diminished with Prazosin therapy.

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. Phillips et al. (2015) revealed similar results during penile vibrostimulation trials, where Prazosin lowered systolic blood pressure when administered without affecting resting blood pressure.

Conclusion

There is level 1 evidence (from two RCTs) (Phillips et al. 2015; Krum et al. 1992), that Prazosin is superior to placebo in the prophylactic management of AD.

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

7.2.6 Phenoxybenzamine (Dibenzyline)

Phenoxybenzamine, a long-acting, adrenergic, alpha-receptor blocking agent, can increase blood flow to skin, mucosae, and abdominal viscera and lower supine and erect blood pressures. The initial dose is 10 mg of Dibenzyline (phenoxybenzamine hydrochloride) bid with increases once daily, usually up to 20-40 mg 2-3 times/days.

Table 19: Phenoxybenzamine (Dibenzyline)

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Lindan et al. 1985; USA Pre-post N=12	**Population:** 12 subjects with tetraplegia **Treatment:** phenoxybenzamine (10 mg bid) and nifedipine (20 mg bid) for 4 days prior cystometry **Outcome Measures:** blood pressure during cystometry.	1. Neither drug effectively prevented AD secondary to bladder filling and a significant number of patients developed troublesome hypotension. 2. Sublingual dose of nifedipine (10 mg) was effective in managing acute attacks of AD.
McGuire et al. 1976; USA Case series N=9	**Population:** 9 individuals with SCI and severe AD. **Treatment:** 6 patients treated daily with phenoxybenzamine (alpha-sympatholytic agent) in doses ranging from 10 to 20 mg. **Outcome Measures:** blood, bladder and urethral pressures.	1. Hypertension, headache and anxiety of AD could no longer be provoked with bladder filling but sweating continued to occur. 2. Mean resting urethral pressure (based on 30 cc bladder volume) decreased after treatment with phenoxybenzamine from 40.6 to 34.0. 3. Mean maximum urethral pressure change with filling decreased after the treatment from +20cmH2O to -30cmH2O.

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) fingings. They reported that after talking phenoxbenzamine 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 (Lindan, Leffler, and Kedia, 1985;McGuire, Wagner, and Weiss, 1976;Scott and Morrow, 1978).

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

7.2.7 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 20: Prostaglandin E2

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Frankel & Mathias 1980; UK Prospective controlled trial N=5	**Population:** 5 patients with complete SCI; age range: 25-37 years; level of injury: C5-T4, 5-108 months post-injury. **Treatment:** trans-rectal electrical ejaculation with and without intravenous administration of Prostaglandin E2. **Outcome Measures**: heart rate, blood pressure, electrocardiogram.	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.

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.

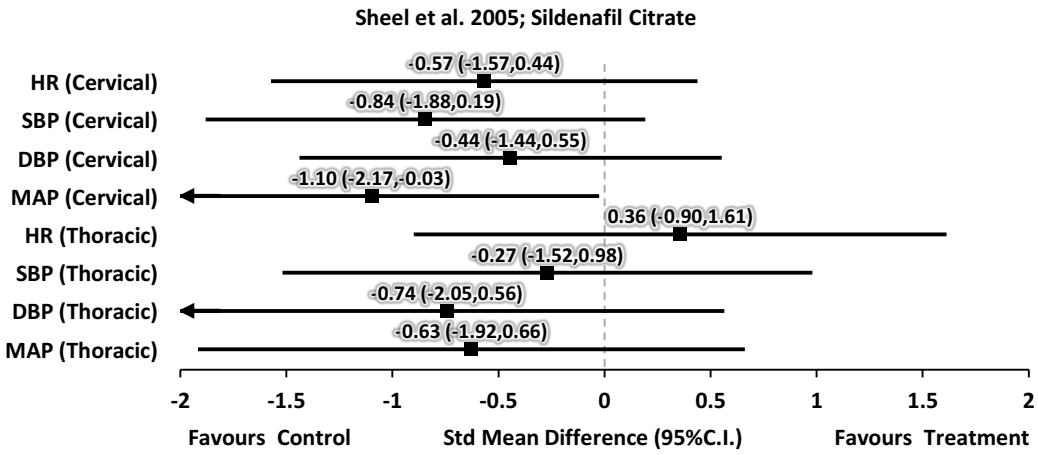
Prostaglandin E2 is effective for reducing BP responses during eletroejactulation.

7.2.8 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 21: Sildenafil (Viagra)

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Sheel et al. 2005; Canada PEDro=5 RCT	**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	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.

N=13	vibratory stimulation. **Outcomes Measures**: ECG, blood pressure.	3. Administration of sildenafil had no effect on HR or BP during AD triggered by penile vibratory stimulation in men with SCI.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data 	

Discussion

The effect of sildenafil on AD was reported in one small RCT with 13 subjects (Sheel, Krassioukov, Inglis, and Elliott, 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.

7.2.9 Other Pharmacological Agents Tested for Management of AD

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), but 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 22: Other Pharmacological Agents Tested for Management of AD

Drug Name	Evidence	Author
Hydralazine (Apresoline)	Expert opinion	Erickson 1980
Beta blockers	Case report	Pasquina et al. 1998
Mecamylamine (Inversine)	Case report	Braddom & Rocco 1991

Drug Name	Evidence	Author
Magnesium sulphate	Case report	Jones & Jones 2002; Maehama et al. 2000
Diazoxide (Hyperstat)	Expert opinion	Erickson 1980
Phenazopyridine	Case report	Paola et al. 2003
Intrathecal Baclofen	Case report	Kofler et al. 2009

8.0 Other Autonomic Dysfunctions

There are a variety of other Autonomic Dysfunctions that can occur after SCI. During the first weeks post-injury, alterations in autonomic function (period of neurogenic shock) require close medical management and may be life-threatening (Guly, Bouamra, and Lecky, 2008;Krassioukov, Karlsson, Wecht, Wuermser, Mathias, and Marino, 2007;Tuli, Tuli, Coleman, Geisler, and Krassioukov, 2007). Low resting arterial blood pressure and severe bradycardia and even asystole can be seen in patients with cervical injuries (Biering-Sørensen, Biering-Sørensen, Liu, Malmqvist, Wecht, Krassioukov, 2017). However, even patients that are not in severe distress need to be carefully monitored for autonomic instability during the initial post-injury period and beyond. We'd like to briefly summarize some of the most common general autonomic dysfunction issues post-SCI (for a more complete discussion of Bladder, Bowel and Sexual Health issues post-SCI, please refer to the specific Chapters in the Evidence section of SCIRE).

8.1 Thermodysregulation

Thermodysregulation is a well-recognized clinical phenomenon after SCI (Colachis and Otis 1995; Schmidt and Chan 1992). It typically occurs in the acute phase of SCI and can potentially last a lifetime. Although thermoregulation is at least in part regulated by autonomic function, the precise mechanisms of thermodysregulation after SCI are not yet fully understood. The degree of dysregulation appears to be related to injury level and perhaps to degree of completeness of SCI, similar to the pattern of AD (Guttman, 1976). Body temperature is under direct autonomic control via hypothalamic regulation; peripheral cold and warm receptors and sensors send messages to the hypothalamus via the spinal cord (Downey, 1973). Temperature is easy to measure and classify, even in the early stages post-injury, and therefore, tracking thermodysregulation may be a useful means of early assessment of autonomic function.

Under normal conditions (that is, when the environment is temperature controlled i.e., not too hot or too cold), people with SCI can have difficulty regulating their body temperature. Individuals with tetraplegia and those with lesions at T6 and above usually exhibit more marked differences in thermoregulation than individuals with paraplegia, most likely due to a lack of hypothalamic connection to the spinal sympathetic circuits and from the standpoint of reduced surface area that can respond (Krassioukov et al. 2007).

Data suggests that patients with tetraplegia after SCI have episodes of subnormal body temperature in a normal ambient environment, and that cold temperatures have a greater negative impact on personal comfort and ability in people with tetraplegia than that of non-SCI controls (Khan et al. 2007; Handrakis et al 2016). There is a clinically recognized, though not widely studied, phenomenon known as "quad fever" where people with tetraplegia or high paraplegia present with a fever exceeding 40 °C (101.5 °F) without a significant rise in core body temperature or an infectious source (Krassioukov et al. 2007).

8.1.2 Thermoregulation during Exercise

Exercise-induced hyperthermia has been more widely studied in recent years. Generally speaking, people with tetraplegia have a greater increase in body temperature with exercise than people with paraplegia even when exercising at similar output/exertion levels, likely due to people with tetraplegia having more difficulty in dispersing endogenously produced heat (Price and Campbell, 2003). It is also common for people with tetraplegia to take longer to cooldown after exercise. Some research suggests the absence of temperature regulation in all levels of complete SCI; Boot et al. (2006) found that mean body temperature can decrease in people with SCI after exercising in the cold, and Price and Campbell (2003) found that neither persons with paraplegia nor those with tetraplegia show any alteration in thigh skin temperature despite changes in core body temperature post-exercise.

Differentiating between those with and without temperature dysregulation may be helpful in discerning those with autonomic incompleteness (whether or not there is motor and sensory completeness). Both core body temperature and skin temperature above and below the level of injury can be helpful in assessing temperature and autonomic function (Krassioukov et al. 2007). Regardless, precautions should be taken for people with SCI when exercising in the cold or in the heat; techniques as common and simple as cool-water foot baths before or during exercise can be successful in restoring a normal body temperature (Boot 2006; Hagobian et al, 2004).

8.1.3 Sweating

Profuse sweating is a common complaint among people with SCI and research has documented that a significant number of people with SCI experience periodic increased sweating associated with AD, orthostatic hypotension, or posttraumatic syringomyelia (Khurana 1987, Jane et al. 1982, Kramer and Levine 1997). Although the most common pattern in SCI is excessive sweating above the lesion level, sweating below the lesion level can also occur. These probably represent different autonomic mechanisms, the pathways of which have not yet been clarified.

8.2 Bradycardia

The central autonomic input (both sympathetic and parasympathetic) is crucial for the cardiovascular control; therefore spinal cord injury can interfere with its function (Henrich 1982; Lehmann et al 1987). Bradycardia, defined as a heart rate of less than 60 beats per minute (bpm), is one common cardiovascular complication that is often lesion-dependent but unique to each SCI. Generally, higher-level injuries along the spinal cord result in a greater degree of cardiovascular impairment; investigators have also reported a higher incidence of bradycardia in persons with tetraplegia than in persons with paraplegia (Mirkowski et al. 2015; Dixit 1995; Biering-Sørensen, Biering-Sørensen, Liu, Malmqvist, Wecht, Krassioukov, 2017). The relationship between injury completeness and resulting cardiovascular dysregulation is less well understood; no clear association has yet been established, even though researchers have reported ECG abnormalities in the SCI population compared with the nondisabled population (West et al. 2013; Prakash et al. 2002).

We would like to emphasize that bradycardia and other dysrhythmias, particularly atrial fibrillation, may also occur during episodes of AD in individuals with high level SCI and may require immediate pharmacological intervention (Pine 1991; Forrest 1991). Current pharmacological management of bradycardia in SCI patients involves the use of different agents including phosphodiesterase inhibitors (e.g., aminophylline, theophylline) and chronotropic agents (e.g., atropine, epinephrine, and norepinephrine) (Mirkowski et al. 2015). Implanting cardiac pacemakers for bradycardia is typically reserved for those who do not respond to pharmacologic treatment (Evans et al. 2014; Franga et al. 2006; Ruiz-Arango et al. 2006; Sadaka et al. 2010; Wood et al. 2014).

9.0 “Boosting” – Autonomic Dysreflexia in Sport

Definition and Background:
In disability sport there is a performance enhancement method known as “Boosting,” when someone intentionally causes a bout of Autonomic Dysreflexia (AD) to improve athletic performance (Gee, West, and Krassioukov, 2015; Mills and Krassioukov, 2011; Blauwet, Benjamin-Laing, Stomphorst, Van, V, Pit-Grosheide, and Willick, 2013).

Some people with SCI, mostly those with injuries at T6 or above, cannot regulate blood pressure and heart rate in the same way as others (West, Romer, and Krassioukov, 2013). Athletes that excel in many sports often have superior cardiac output and/or oxygen uptake. During competition a wheelchair athlete’s heart rate may not increase according to the body’s demands, leading to low blood pressure, fatigue, and often a loss of endurance and poor performance.

What Happens:
Some athletes have learned they can subvert these cardiovascular dysfunctions and increase their blood pressure and other cardiac outputs (in the short-term) by causing some pain or discomfort in an area below their injury. They may do this by:

- Clamping of the urinary catheter to produce bladder distension
- Excessive tightening of the leg straps
- Twisting and/or sitting on the scrotum
- Breaking their big toe before the competition
- Abdominal binders or pressure stockings on legs

Consequences:
Athletes with SCI who self-inflict physical suffering in order to improve athletic performance take tremendous health risks (i.e., hypertension, cerebral hemorrhage, stroke and sudden death).

In a study of 99 athletes with SCI, 54.5% had previously heard of AD while 39.4% were unaware; 16.7% (all males) had used AD to enhance performance, despite participants reporting that AD is somewhat dangerous (48.9%), dangerous (21.3%) or very dangerous (25.5%) to health. These findings indicate the need for educational programs directed towards enhancing the AD knowledge of rehabilitation professionals, coaches and trainers working with SCI individuals (Bhambhani et al. 2010).

The International Paralympic Committee considers AD doping and has banned its use. Any deliberate attempt to induce AD, if detected, will lead to disqualification from the sporting event and subsequent investigation by the IPC Legal and Ethics Committee.

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