Modulating spinal reflex pathway for treatment of detrusor overactivity in patients with spinal cord injury by stimulating sacral afferents at sole of foot: A pilot study

Dissertation submitted to

the Tamil Nadu Dr. M.G.R. Medical University

in partial fulfilment of the requirement for

M.D. branch XIX – (Physical Medicine and Rehabilitation)

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Dr.Anna Pulimood

Principal

Christian Medical College

Vellore, 632 002

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Dr. Raji Thomas

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DECLARATION

I hereby declare that this dissertation titled "Modulating spinal reflex pathway for treatment of detrusor over activity in patients with spinal cord injury by stimulating sacral afferents at sole of foot" is a bona fide work done by me under the guidance of Dr. Jacob George, Professor, Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore. This work has not been submitted to any university in part or full.

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INDEX: **Topic Page no.**

Abbreviations

CIC – Clean intermittent catheterization

CMG - Cystometrography

C*v*C*i* - Cumulative voiding chart index

PTN - Posterior Tibial Nerve

SCI – Spinal cord injury

US - Ultrasonography

UTI – Urinary tract infection

PVR- Post void residual urine

Abstract

Title of Study: Modulating spinal reflex pathway for treatment of detrusor overactivity in patients with spinal cord injury by stimulating sacral afferents at sole of foot.

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Name of Candidate: Dr Abhinav Singh

Degree and Subject: M.D PMR

Name of Guide: Dr. Jacob George

Name of Co-Guide: Dr Rajdeep Ojha

Aim: To reduce detrusor overactivity by modulating spinal reflex pathways using electrical stimulation at sole of foot in patients with spinal cord injury.

Methods: Twenty patients, meeting key inclusion/exclusion criteria, on clean intermittent catheterization having Cystometrogram(CMG) proven detrusor overactivity with intact ankle-jerk and complaints of at least one leak per day consented for the study. All the patients maintained voiding chart one-week prior and two-weeks during the treatment. Cystometrogram was done on day 1 and 15. Electrical stimulation was given half-an-hour daily for two-weeks keeping same parameters as our previous study(1). Anode and cathode were placed at metatarsal and arch of foot respectively. In-house developed stimulator costing less than Rs2000, was used. Satisfaction questionnaire were

taken on day 15. Voiding chart data was analyzed using novel Cumulative Voiding Chart Index(C*v*C*i*) developed at Department of PMR, CMC Vellore. Wilcoxon signed-ranked test was used for CMG data while Binomial distribution for voiding chart data as test of significance. The p-value<0.05 was considered as significant. Study was approved by Institutional review board and ethics committee(CMC/IRB/11061/2017/12/20).

Results: Post-treatment the p-value for improvement in maximum detrusor pressure(p-value-0.03) and cystometric capacity(p-value-0.04) was found to be statistically significant while p-value of reflex volume(p-value-0.13) was not significant. Eighteen patients showed improvement in bladder function and two subjects did not show any signs of improvement as reported by C*v*C*i* score derived from voiding chart.

Conclusion: Neuromodulation by surface electrical stimulation at sole of foot is simple, non-pharmacological, non-invasive, inexpensive, promising alternative treatment modality for reducing detrusor overactivity.

Key words: Spinal cord injury, Detrusor Overactivity, Neuromodulation, Cystometrogram, Surface electrical stimulation, Urinary Incontinence

Aim: To reduce detrusor overactivity by modulating spinal reflex pathways using electrical stimulation at sole of foot in patients with spinal cord injury.

Objective:

1. To study short-term therapeutic effect of electrical stimulation of tibial nerve at the sole in modulating spinal reflex pathways and its effect on detrusor overactivity in patients with spinal cord injury.
2. To study the effect of new treatment modality on reduction in number of leaks as reported by voiding chart.
3. To study the effect of new treatment modality on reduction in detrusor overactivity by analyzing urodynamics report.
4. To improve the quality of life of patients with spinal cord injury by reducing urinary incontinence.
5. To come-up with the new quantitative method of analyzing voiding chart data to compare the efficacy of the treatment.

Hypothesis: Electrical stimulation of somatic afferents (in our case branch of tibial nerve, at the sole of the foot) which have the same root level as the urinary bladder (i.e. S2–S4) can result in neuromodulation leading to a reduction in spasticity of the detrusor muscle.

Introduction

Spinal cord injury is an ailment that directly or indirectly affects all body system. One of the most distressing complaints about patients with Spinal cord injury (SCI) is urinary dysfunction. In SCI patients, the loss of supraspinal control can be responsible for overactivity of detrusor muscles, leading to small bladder capacity. As a result of which patient may have high bladder pressure, vesicoureteral reflux and renal impairment and bladder incontinence. Clean intermittent catheterization (CIC) along with antimuscarinic drugs is the gold standard for the management of spinal cord injury with neurogenic bladder. Sacral neuromodulation, tibial nerve stimulation, and pudendal nerve stimulation considered an option for the management of neurogenic bladder secondary to SCI; but, because of invasive nature, it has its limitations. Stimulation of the somatic afferent pathways can be an important factor in the efficacy of neuromodulation. Results of the phase 1 study conducted in our department in the year 2009-2011 (IRB No CMC/IRB/6735/2008/12/18) showed improvement in urinary leaks as per voiding chart after two weeks of stimulation of the posterior tibial nerve. In our study, we tried to find if the electrical stimulation of the branch of tibial nerve at the sole of foot (i.e medial planter nerve) can help in modulating spinal reflex pathways for reducing detrusor overactivity.

Review of literature

Spinal cord injury (SCI) drastically changes a life. Changes in function due to the spinal cord injury can be, either temporary or permanent. These changes translate into a loss of muscle function, sensation, or autonomic function. It affects physical, social as well as psychological aspects of a person. Spinal cord injury is an ailment that directly or indirectly affects all body system.

Symptoms of spinal cord injury vary widely. Level, site and severity of damage of spinal cord determine symptoms. Patients with spinal cord injury presents with paralysis, pain, sensory loss and bladder/ bowel incontinence. Paralysis can be flaccid or spastic depending on upper motor or lower motor neuron injury. Common post SCI complications are muscle atrophy, pressure sores, urinary tract infections, and respiratory problems. Spinal cord injury and its complications were first described in 17^{th} century. It was called an injury that cannot heal (2). In 2007 it was estimated that globally, there would have been between 133 and 226 thousand incident cases of TSCI from accidents and self-harm/violence. Twenty-one per million cases were estimated in South Asia(3). World over it is estimated that 10.4 to 59 people per million per year are getting spinal cor injury due to one reason or the other (4). It is estimated that 1800 per million in the US to 236 million in India are affected with SCI(5). Males account for the majority of traumatic spinal cord injuries. Young male below 30 years of age are most common victims of this disease(6). The increase in number of SCI cases are most commonly

attributed to road traffic accidents and sports injuries(7). The spinal cord has four regions, named after the vertebrae they travel through. They are cervical, thoracic, lumbar and sacral. Cervical vertebrae are involved in approximately half of traumatic SCI, followed by thoracic and then lumbosacral vertebrae. Among Cervical vertebrae, C5 segment is the most commonly affected followed by C4, C6 and C7(8).

Complications of spinal cord injury

Complications after spinal cord injury can affect any organ system in the body. The leading cause of death in the first year following injury are respiratory complications.. According to a cohort from a model of SCI care systems and Shriner's Hospitals, respiratory complications accounts for 37% of deaths and 21% of deaths after the one year of injury(9). Urinary tract infections, infected pressure ulcers and respiratory tract infections can lead to cardiac complications and septicemia(10). Genitourinary complications after SCI has decreased considerably due to the scientific advances in the management of the urological symptoms. The urologic complications are mostly secondary to the neurogenic bladder. It includes UTI, prostatitis, hydronephrosis, epi-didymo orchitis, urethral erosions and strictures, renal and bladder calculi, peno-scrotal fistulas, bladder cancer and renal failure(10).

According to Model Spinal Cord Injury Systems Database, USA, 55% of patients needed rehospitalization within a year of SCI(11). Genitourinary and respiratory complications along with pressure ulcers were common cause leading to hospitalization. SCI with

advanced patient age, added to the risk of complications requiring hospitalization. One of the most distressing complaints about patients with SCI is urinary dysfunction. Bladder incontinence is one of the biggest hurdles in rehabilitation(12).

Urinary system

It is divided into upper and lower urinary tract. The Kidneys, and the ureters forms the upper tract or upper urinary tract. Urinary bladder, internal urethral sphincter, external urethral sphincter and the urethra constitutes lower urinary tract. The end products of metabolism and excess fluid are filtered by upper tracts. It excretes filtrates in the form of urine into the lower urinary tract through the ureters, mainly into the bladder. Lower tract is mainly for storage and voidng of urine.

Kidney: Anatomy and physiology

The workforce for the urinary system is a kidney. It is a filter used to purify the blood. They also regulate blood volume, pH, pressure, osmolality as well as produce hormones. It is a retroperitoneal organ, located between T12 and L3 vertebrae and partially protected by floating ribs. Right Kidney is pushed down by the liver, so it is slightly lower than the left kidney. In between each kidney is an indentation forming renal hilum. Renal hilum is an entry and exit point for renal ureter, renal arteries, renal vein, lymphatics, and nerves. It is surrounded by three layers of tissues, outer renal fascia, the middle adipose capsule is fatty layers and an inner layer of the dense renal capsule.

Renal fascia is a thin layer of dense connective tissue that adheres to the surrounding. Adipose tissue is a fatty layer that protects the kidney from trauma. Renal capsule is the smooth, transparent dense connective tissue that gives kidney its distinctive shape.

Cross-section of the kidney has an outer cortex and an inner medulla. The renal cortex is made up of outer cortical zone and inner juxta-medullary zone. Part of renal cortex extending down into the medulla is called renal columns.

The renal medulla is made 15-20 renal pyramids and separated by renal columns. The base of pyramids faces towards the cortex. Tip of pyramids is called renal papilla or nipple and face towards the centre of the kidney. It projects into minor calyces. Minor calyces join to form major calyces which open into the pelvis. Urine collects in renal pelvis and heads into the ureter.

An adult kidney filters about 150 litres of blood every day, i.e. kidney filters blood of the whole body at least 30 times per day or more than once every hour.

Kidney gets about 20 -25% of cardiac output. To reach kidney blood flows from aorta to the right and left renal artery, respectively. Inside the kidney, they divide into segmental arteries, which further divides into interlobar arteries and pass through the renal columns to form arcuate artery. Arcuate artery goes over the pyramid and then into the cortical radiate artery, which supplies cortex. Cortical radiate artery continues to divide and form afferent arterioles. Afferent arterioles form capillaries into the glomerulus. Glomerulus enters into efferent arterioles which divide to form peritubular capillaries. Peritubular

arteries reunite to form veins then into arcuate veins and inner lobar veins and finally into left and right renal veins. Renal veins connect to inferior vena cava.

The basic unit of the kidney is nephron. Each kidney had millions of nephrons. Each nephron has renal corpuscles and renal tubule. Blood filtration starts in renal corpuscles, which is made of glomerulus and Bowman's capsules. The glomerulus is made of tiny arterioles while Bowman's capsule made of renal cells surrounding the glomerulus. When blood enters glomerulus, water and solutes pass through the endothelium, basement membrane and epithelium to collect in Bowmans space and forms filtrate. Epithelium of nephrons made of special cells called podocytes. In between podocytes are infiltrate sluts which allow only water and glucose to pass through and are impermeable to proteins and RBCs.

As infiltrate leaves the Bowman capsule, it reaches renal tubules. Peritubular capillaries surround renal tubules. The renal tubule divide into proximal tubule, the loop of Henle, distal convoluted tubules (DCT), collecting ducts and minor calyces. The loop of Henle is made up of descending and ascending limb. In renal tubules, the filtrate is fine-tuned depending on the needs of the body. Water and electrolytes pass to and fro between filtrate of renal tubules and blood in peritubular capillaries.

Each nephron has a juxtaglomerular complex located between DCT and afferent arteriole. It regulates blood pressure and glomerular filtration rate. There are three types of cells in juxtaglomerular complex viz macula densa cells, extraglomerular mesangial cells and juxtaglomerular cells. Macula densa senses low sodium and chloride level and sends a

signal to juxtaglomerular cells located in walls of afferent arterioles. Juxtaglomerular cells sense low blood pressure and secretes an enzyme called rennin. Rennin increases sodium resorptions and causes constriction of blood vessels. Sodium resorptions raise blood volume and cause constriction of the blood vessel. Constriction of blood vessels raises blood pressure.

Millions of nephrons make urine, and from each nephron, urine flows into minor calyces, major calyces and finally into the pelvis. From there it goes down to ureter.

Ureter has muscular lining and helps to pull down urine. Ureter inserts into vesicle at ureterovesical junction. Insertion is at a sideways angle to prevent backflow of urine into ureter when the bladder is full. It is one way valve which connects bladder and ureter and prevents refluxing back of urine.

Bladder: Anatomy

The bladder is balloon like reservoir for collection of urine. It is a muscular structure that that has capcity to expand and contract. It lies in the pelvis and distends and expands with collection of urine. Expansion of bladder is mainly anterosuperiorly.

Bladder is divided into 4 parts: (1)Fundus (2) Base (3) Neck and (4) Apex. It has one superior surface and two inferolateral surfaces(13).

Bladder has four layers: (1) serous, (2) muscular,(3) sub-mucous and (4) mucous. The peritoneum gives rise to serous layer. Muscular wall of serous layer has folds called rugae. Rugae contracts when the bladder has to be emptied and relaxes during filling.

The muscular layer consists of three smooth muscular fibres:

(1) external: consisting of longitudinal fibres

(2) middle:consisting circular fibres

(3) internal layer: consisting of longitudinal fibres.

The external layer consists of the detrusor muscle. The internal urethral sphincter is made from fibers of middle circular layer. The obliquity of the ureters during bladder contraction is maintained by oblique fibres originating behind the orifice. There are two bands of oblique fibers. It also prevents urine reflux into the bladder. In between the muscular and mucosal layer is submucosal layer, which is a connecting cushion between them .

The transitional epithelium covers the mucosal layer(14). Transitional epithelium helps bladder in stretching and maintaining a barrier between urine and body.

The bladder has mucosal layers, consisting of transitional epithelium. There is a thick muscular layer called detrusor muscle, which helps in bladder contraction. It has a thick fibrous adventitia over outer layer.

In women, the bladder is in front of the vagina, uterus and rectum. In men, it is just in front of the rectum. On average bladder can hold about 750 ml of urine. However, it holds less in women due to surrounded by the uterus, especially during pregnancy.

The bladder has a smooth triangular region called trigone. Two junctions being ureterovesical junctions and third inter urethral orifice. At urethral orifice, bladder meets urethra. Trigone region is very sensitive to expansion. Once a certain limit reached, it sends a signal to the brain to pass urine.

The urethra is a thin muscular structure that drains urine from the bladder. It starts from the internal urethral orifice in the bladder and end in the external urethral orifice. It measures about 18-20cm in males. Females urethra is almost $1/4^{th}$ length of that of males. It starts from internal urethral orifice to external urethral orifice. In male, urethra first passes through the prostate, where it is called prostatic urethra. Then passes through deep layers of peritoneum where it is called intermediate urethra, and then it passes through the penis where it is called spongy urethra. The male urethra is also used during ejaculation. Semen enters into the urethra through the ejaculatory duct which opens into the prostatic urethra. In the female, the urethra runs through the perineal floor of the pelvis. It exists between two labia minora, above the vaginal opening and below the clitoris. Detrusor muscle thickens to form internal sphincter around the internal orifice. There is external urethral sphincter at the level of the urogenital diaphragm, which is under voluntary control. The mucous membrane is in continuity through out the urinary

system i.e urethra, bladder, ureters and kidneys. The mucous membrane in urethra is supported by submucous tissue(14).

Active urination requires closed coordination between central nervous system and muscles of the bladder. Pressure on wall increases, once the bladder has 300-400ml of urine. It sends a signal to the micturition centre of the brain.

Physiology of micturition

The bladders is made of detrusor muscle which can contract and relax. There are two sphincters in male: internal and external. In between these two sphincters, there is prostate gland. The prostate gland is only found in male and has a role in sperm activation. When there is prostate hypertrophy, it can obstruct urethra and hence problem in urinating. Female don't have internal sphincter, but they do have external sphincter. The urethra of the female is shorter than the male. As a result, there is more chance of urinary tract infection.

The receptors found in urinary tract play a major role in micturition and holding in urine. Receptors found on bladder include muscarinic receptors (M3 receptors) and beta-adrenergic receptor (β3). Alpha-adrenergic receptors (**α**1) found on the internal sphincter and nicotinic receptors on the external sphincter.

Control of micturition

The central nervous system controls micturition. Micturition centre is located in Pons and transmits a signal through the spinal cord. Signals from CNS is sent to the urinary system through nerves. There are three important afferent nerve fibres which control the micturition.(Figure 1) The first nerve comes from the sacral region of the spinal cord called pelvic nerve, which is parasympathetic nerve. It is not under our control. The parasympathetic neurons arise from the sacral centres. The axons of parasympathetic neurons are located in the pelvic nerves, while that of postganglionic fibres are present in the intramural vesical ganglia. The somatic motor centre is present in Onuf's nucleus. It is present in the ventral horn of the sacral spinal cord. Onuf's nucleus supplies the external sphincter through the pudendal nerve. Acetylcholine is released by it which binds with M3 receptors. Second nerve coming out of the sacral region is pudendal nerve. It is a somatic nerve and under our control. The pudendal nerve also releases acetylcholine and binds at nicotinic receptors of the external sphincter. It causes the external sphincter to contract. The third nerve is a hypogastric, which is a sympathetic nerve coming from the thoracic, lumbar area. It supplies through the hypogastric and pelvic nerves. Axons of A-delta fibres are small myelinated one while that of C-fibres are unmyelinated. Both A –delta and C-fibres carry the sensory afferents. Cell bodies of pelvic nerve is situated in the sacral root ganglia. Because of pudendal nerve activation, one is able to hold urine. It synapses in ganglion which passes information to post sympathetic fibre. Hypogastric nerve releases neurotransmitter noradrenaline. It targets

two things, β3 receptors and **α**1receptors.The synergistic detrusor-external urethral sphincter function is coordinated by pontine micturition(15). Spinal neurons present in the dorsal commissure, superficial dorsal horn and parasympathetic nucleus controls the function of lower urinary tract.

Glutamate is the excitatory transmitter, and Gamma-aminobutyric acid and Glycine are inhibitory neurotransmitters (16).

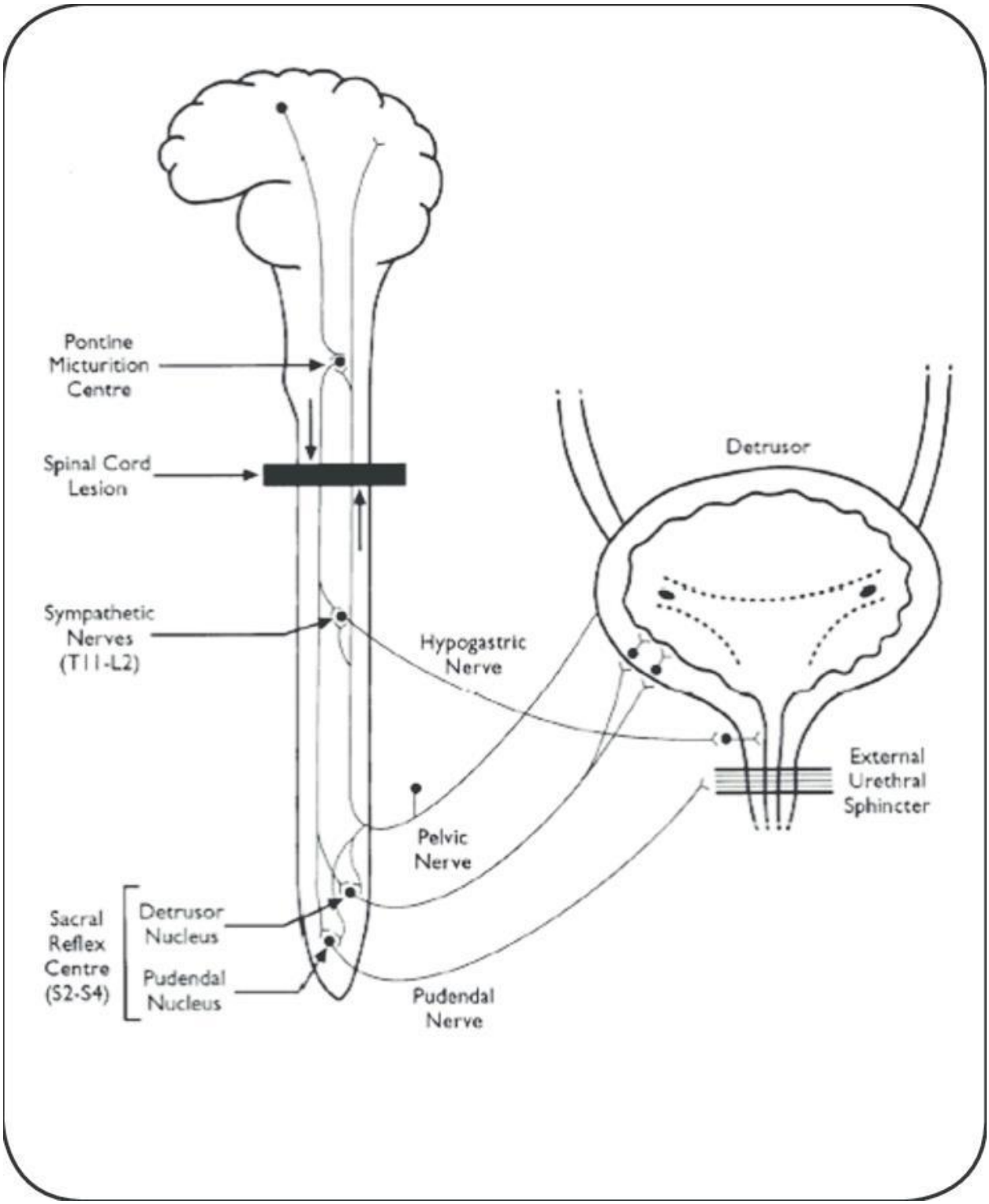

Figure 1 Neural control of micturition

The supraspinal structure involved in the control of micturition is pontine micturition centre. It is also called as medullary dorsomedial pontine tegmentum.

Activation of brain regions during lower urinary tract function has been reported on the basis of Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). In the storage phase of micturition, the peri aqueductal grey (PAG) area receives afferent signals from bladder. Then it is relayed through the hypothalamus to the anterior cingulate cortex, the insula and the prefrontal cortex. The prefrontal cortex, hypothalamus, insula and anterior cingulate cortex are PAG inhibitors and thereby inhibiters of the pontine micturition centre. PAG is inhibited by prefrontal cortex during voiding. The hypothalamus stimulates the PAG and the pontine micturition centre which send excitatory signals to the sacral spinal cord. Sacral spinal cord controls the contraction of the detrusor and relaxation of the urethra(17).

Receptors and neurotransmitters on the bladder wall are: (1) muscarinic,(2) nicotinic, (3) alpha and (4) beta-adrenergic receptors. The bladder, the trigone, bladder neck and the urethra has cholinergic muscarinic M2 and M3 receptors. Functionally M3 receptors are more important than M2. The striated sphincter mainly consists of cholinergic nicotinic receptors (15). The trigone, bladder neck and the urethra has **α**1adrenergic receptors Subgroups of **α**1 receptors, help in increased specificity of therapeutic agents. The paravesical and intramural ganglia consists of nor epinephrine secreting nerve cells. Nor epinephrine (excitatory) maintain continence by contraction of the bladder neck and smooth muscle of urethra. β 2 and β 3 adrenergic receptors in the body and neck of the

bladder are inhibitory. They produce relaxation of bladder neck during the initiation of voiding and relax the bladder during the filling phase for storage of urine(15).

Urethral contraction is mainly controlled by nor-epinephrine via **α**1receptors. Acetylcholine action in the pelvic ganglia relaxes urethral smooth muscle. Release of nitric oxide in pelvic ganglia,leads to the relaxation of the muscle. Prostaglandins also helps in relaxation of thesmooth muscles of urethra. Serotonin causes urethral muscle contraction, as a result it can be used in treating open bladder neck (15). Opiate receptor activation in the brainstem and spinal cord can cause retention of urine. Inhibitory or excitatory effects of neurotransmitters are based on their site of action. Detrusor effect in the midbrain is inhibited by serotonin. This is reason serotonin blockers like tricyclics are used for treatment of nocturnal enuresis. Serotonin and nor-epinephrine re-uptake inhibitors (SNRI) prolong its effect in the Onuf's nucleus, leading to increased activity of the external urethral sphincter. Signals travel to and fro from the brain to urinary bladder through the spinal cord.

Neurogenic bladder after SCI

A malfunctioning urinary bladder due to neurologic dysfunction is called neurogenic bladder. It is most commonly due to spinal cord injury, which can be either due to traumatic or non-traumatic causes(18).

The outcome of the SCI on the lower urinary tract depends on the (1) aetiology (2) level of injury (3) duration of injury and (4) severity of the injury.

Immediately after spinal cord injury, there is a period of bladder areflexia. It is during spinal shock and leads to urinary retention. The duration of areflexia depends on the period of the spinal shock phase. It varies from few hours to few weeks(19). Activation of low threshold A-delta fibres initiates micturition reflex. After SCI, micturition reflex depends on C-fibres. C fibres has been found to be Capsaicin sensitive. Reduction in bladder overactivity has been demonstrated by intrathecal Capsaicin administration.(20). The change in physiology of the lower urinary tract and the micturition reflex leads to complications like UTIs and others.

Classification of neurogenic bladder done in various ways. They are:

1. Anatomic classification: it is based on the anatomic level of injury, as shown in the figure 2.
2. Functional classification is based on cystometric findings. It has five basic groups:(1) reflex (2) uninhibited, (3) autonomous, (4) motor paralytic and (5) sensory neurogenic bladders.

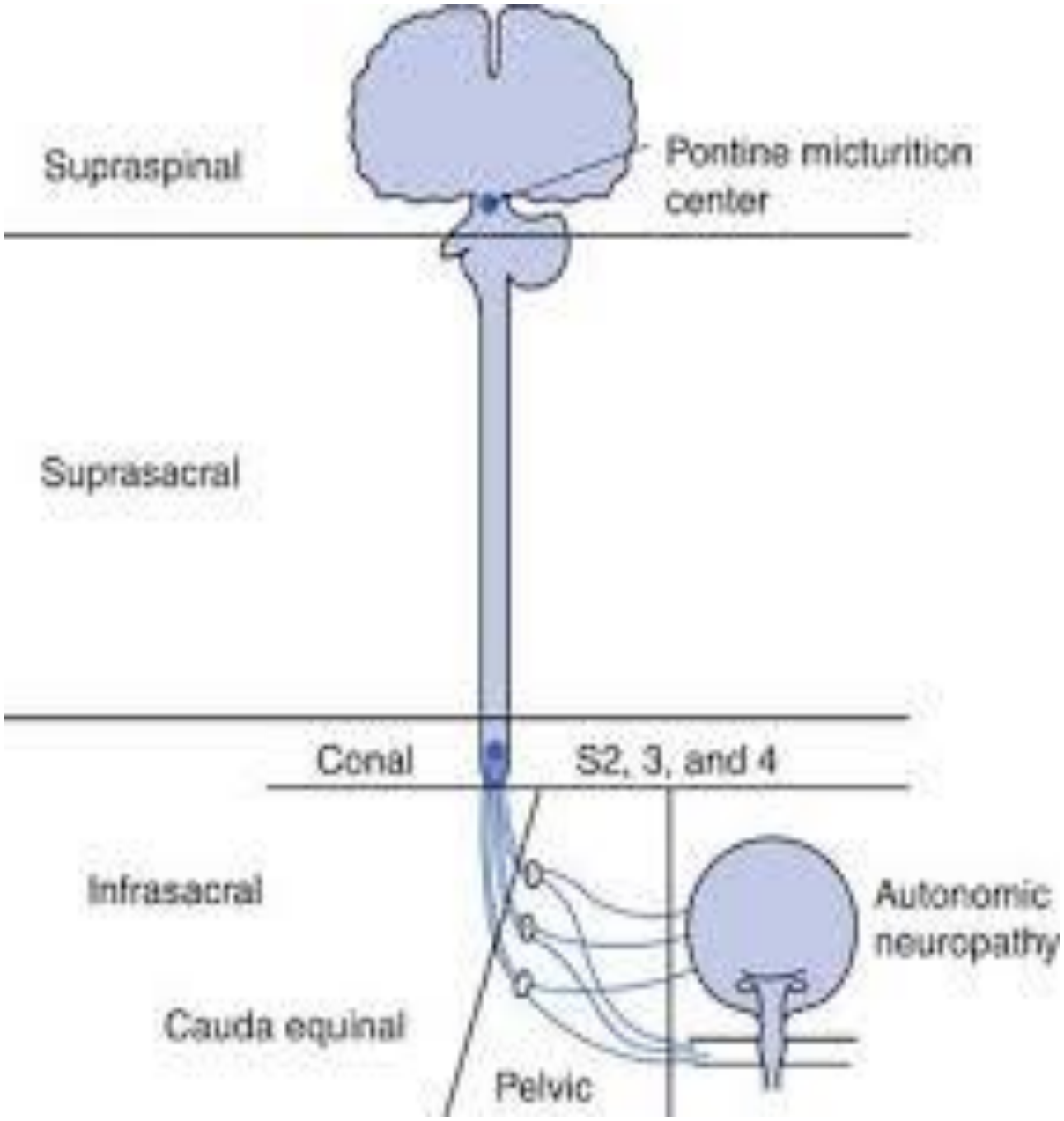

Figure 2 Anatomic classification of Neurogenic bladder

It is based on the conventional urodynamic study. It is categorized according to the

(1) passive storage ability of the bladder

(2) activity and coordination of the detrusor and sphincter.

Combination of both anatomic and functional classifications is used in clinical practice. Clinical management is mainly based on functional changes ,demonstrated by urodynamic testing (15).

Table 1. Functional classification

Type of failure	**Bladder factors**	**Outlet factors**
Storage failure	Detrusor hyperactivity	Denervation of pelvic floor
	Low compliance	Bladder neck descent
		Failure of Intrinsic bladder neck sphincter
Voiding failure	Low compliance	Detrusor-sphincter dyssynergia(DSD)
	Hypocontractility	Non relaxing voluntary sphinchter Mechanical obstruction (Benign prostatic hypertrophy or stricture)

Complications of neurogenic bladder

Complications related to neurogenic bladder were the leading cause of morbidity and mortality in SCI patients till middle of the last century. Due to improvement in management techniques, mortality in patients with neurogenic bladder has decreased significantly. In spite of all advances complications due to neurogenic bladder are still prevalent(21).

Urinary tract infections (UTIs)

Among patients with neurogenic bladder UTIs is most common complications. Risk factors include incomplete bladder evacuation and significant post-void residual volume. Blockage of ejaculatory and prostatic duct due to long term catheterization can cause epididymorchitis, seminal vesiculitis or prostatitis. Symptomatic UTI are less common compared to asymptomatic catheter associated bacteriuria. Evidences about incidence of UTI among patients using different strategy for intermittent catheterization are limited. It doesn't get affected if the sterile or clean technique, single or multiple-use catheters, coated or uncoated catheters or any other strategy is used(22).

Urethral strictures and false passages are common complications due to long term use of CIC. Complications can be reduced by good patient education leading to good compliance by using proper material and technique(23).

Vesicoureteric reflux

Reflux of urine from the bladder into the ureters is called Vesicoureteric reflux. It is diagnosed by cystogram and video urodynamic study. It is due to failure to maintain optimal bladder pressure-volume profile. Suprasacral SCI patients are more prone to reflux, however, it can occur in any type of neurogenic bladder. Due to persistent reflux,patients can have recurrent urinary tract infections ,which may predispose to the formation of bladder calculi also. It can lead to renal deterioration if not managed timely. Severe renal compromise in SCI patients can subsequently lead to death(24).

Hydronephrosis

Increased detrusor pressure in a poorly compliant bladder causes dilatation of the upper urinary tract. It can be associated with or without vesicoureteric reflux. It is associated significant morbidity and mortality. In neurogenic bladder, vesicouretric reflux further contributes to hydronephrosis.

Any obstruction to ureters, detrusor sphincter dyssynergia or bladder calculi can cause hydronephrosis. It is diagnosed by US, CT or MRI scans..

Hydronephrosis is classified as:

1) mild
2) moderate
3) severe.

The Society of Fetal Ultrasound (SFU) has developed a grading system for hydronephrosis(25), initially intended for use in neonatal and infant hydronephrosis, but is now used for grading hydronephrosis in adults as well:

1) Grade 0 − Normal examination without dilation of the renal pelvis
2) Grade I – Mildly dilated renal pelvis only
3) Grade II − Moderately dilated renal pelvis including a few calyces
4) Grade III − Dilated renal pelvis with visualization of all the calyces, which uniformly dilated, and normal renal parenchyma
5) Grade IV − Similar appearance of the renal pelvis and calyces as grade III, with thinning of the renal parenchyma

Calculi

Loss of calcium from the bones after SCI often leads to hypercalciuria. It can further lead to the formation of renal calculi. Upper tract calculi found after 10 years of SCI are mostly secondary to infection. Incidence of bladder calculi is about 2.3%,in the first 9 months of starting clean intermittent catheterization. Compared to CIC prevalence of claculi is higher among patients on the indwelling catheter (15).

***Autonomic Dysreflexia*(AD)**

It is paroxysmal hypertension, low heart rate, increased sweating above the neurological level. It can be associated with restlessness, headache and piloerection. Patients with spinal cord injury above T6 neurological level are at risk of autonomic dysreflexia.

Catheter block leading to distension of the bladder is a common cause of autonomic dysreflexia(15).It can also occur due to impacted stool, constipation, anal fissure or impacted toe nail.

Evaluation of Neurogenic bladder

Neurogenic bladder evaluation needs careful history and a proper examination.

Lower urinary tract symptom classification: According to the International Continence Society (ICS)– Fact sheet, 2015, the lower urinary tract symptoms are classified on the basis of:

(1) bladder capacity/storage symptoms

(2) Voiding symptoms

(3) Post micturition symptoms(26).

Storage symptoms:

Patient mainly present with increased day time-frequency. It include daytime frequency and nocturia. They considers it as voiding too often by day.

Nocturia **:** patient wakes up once or more than once in night for voiding.

Urgency : patient has a sudden compelling desire to pass urine.It is difficult to postpone.

Urinary incontinence: patient has involuntary leak of urine.

Urge incontinence: patient has involuntary urine leakage that accompanies or precedes urgency.

Stress urinary incontinence: patient has involuntary leakage of urine on exertion. It is most commonly associated with coughing, sneezing or lifting the weight.

Mixed urinary incontinence: patient has involuntary urine leakage but it is associated with urgency and exertion.

Nocturnal enuresis: patient has loss of control of urine during sleep.

Continuous urinary incontinence: patient has continuous leakage of urine.

Bladder sensation is defined:

- **Normal**: patient is aware of bladder filling and increasing sensation up to a strong desire to void.
- **Reduced** : patient is aware of bladder filling but does not feel a desire to void.
- **Absent** : patient has no sensation of bladder filling or desire to void.
- **Increased :** patient has an early and persistent desire to void.
- **Non-specific** - patient has no specific bladder sensation. They perceive bladder fullness as abdominal fullness or spasticity.

Voiding symptoms:

Patient experiences it during the voiding phase.

Hesitancy : patient has difficulty in initiating micturition. It causes delay in the onset of voiding after the person is ready to pass urine.

The slow stream: patient feels reduced flow of urine. They have perception of reduced urine flow on voiding compared to previous performance.

The intermittent strea : urine flow stops and starts during micturition. It occurs on one or more occasions.

Straining: patient has to apply the muscular effort to initiate, maintain or improve the urinary stream.

Terminal dribble: The flow slows down to a trickle/dribble at the final part of micturition.

Post micturition symptoms

Post micturition symptoms are experienced immediately after micturition. The feeling of incomplete emptying is a self-explanatory. It is feeling experienced by patient after voiding.

In post micturition dribble, patient has involuntary loss of urine immediately after voiding.

Lower urinary tract pain symptoms:

It is abnormal sensations felt by the patient. Patients present it as pain, pressure or discomfort. Pain can be felt during storage or voiding phases of the bladder cycle. It should be characterized by:

1) Type
2) Duration
3) Frequency
4) Precipitating factors
5) relieving factors and location

Urethral pain : Patient feels it in the urethra.

Bladder pain: Patient feels it suprapubically or retropubically .It increases with bladder filling and may persist during voiding.

Scrotal pain: Patient feels it in the testis or epididymis, cord structures or scrotal skin.

Vulval pain : Patient feels it in and around the external genitalia.

Vaginal pain : Patient feels it above the introitus and internally.

Pelvic pain : Patient feels it in pelvic region. It is not well defined in relation to micturition cycle or bowel function.

Perineal pain : Male patient feels it between the scrotum and anus. In females it is felt between posterior fourchette and the anus (26).

Presenting symptoms:

The presenting symptoms are multifactorial. It depend on the following factors

1) cause of the injury
2) duration and extent of the injury
3) level of spinal cord injury
4) neurologic recovery after the initial trauma.

After the spinal shock phase, symptoms vary to great degree especially in an upper motor neuron type of bladder. Patient may present with impaired bladder sensation and ability to void, intermittent non-stress urinary incontinence, hesitancy, straining, urgency, diminished or interrupted stream.

In lower motor neuron type of bladder, bladder sensation will be present. Other symptoms may include difficulty in voiding normally, stress urinary incontinence and necessity to apply abdominal pressure for emptying the bladder.

The history should include the following (27) :

1. Voiding pattern prior to injury
2. Presence or absence of bladder sensation
3. Lower urinary tract symptoms
4. Mode of voiding
5. Frequency of voiding
6. difficulties during voiding

7. Incontinence
8. Relevant review of other systems including history of Diabetes, hypertension

Physical examination:

A meticulous and detailed neurological examination must be done. It should include deep tendon reflexes, plantar responses and presence or absence of clonus in lower limbs. Bulbo-cavernous reflex in males and clitoral- cavernous reflex in female should be examined. The sensory examination should include sacral dermatomes i.e perianal sensation, deep anal pressure, voluntary anal contraction. (15).

Voiding Chart/Bladder diary:

Voiding chart help in assessment of neurogenic bladder symptoms. Frequency volume chart maintain the voided volumes and micturition time chart records the timing of each micturition. Symptoms like urgency, pain, incontinence episodes and pad usage can be added in the diary. Following inferences are made from voiding chart:

1) average of voided volume
2) voiding frequency
3) day/night urine production
4) nocturia .

Correlation of symptoms and objective verification can be done on the basis of voiding chart. It prevent overfilling of the bladder during urodynamic study by providing control

values (15). Patients who are doing clean intermittent catheterization (CIC), CIC timing is considered as Micturition time.

Diagnostic tests:

Urologic testing should be individualized to each patient. It depends on symptoms and neurological condition of patients. Lower urinary tract evaluation should include routine urinalysis, urine culture, and measurement of post-void residual volume. In case of incomplete voiding, upper tract changes or recurrent urinary tract infection can be present. In such cases complete urodynamic evaluation may be required. The urodynamic study is used for confirmation of the type of bladder as determined by clinical examination

The urodynamic results are not condition specific. It cannot be used to determine the level of the neurologic lesion. For example, Cauda equina bladder may show low compliance with detrusor overactivity. while suprasacral neurogenic bladder in a complete spinal cord injury can be areflexic (19).

Upper tract tests:

Ultrasonography (US)

Ultrasonography is a cheap and low-risk test for the evaluation of urinary tract. It has limited role in evaluation of acute ureteral obstruction, for which other investigations are required. The US can be used for imaging hydronephrosis, dilation, scarring, renal mass

(both cystic and solid), chronic obstruction as well as renal calculi. Bladder wall thickness, irregularity and presence of calculi can be visualized in a filled bladder.

Plain radiography of the kidneys, ureter and bladder (KUB)

Kidneys, ureters and bladder (KUB) X-ray combined with the US help in identifying calculi which may be missed in the ultrasonography alone.

***Computed tomography* (CT)**

In acute obstruction of ureters due to calculi CT scan of KUB is useful in the evaluation of the upper tracts. In such cases contrast agent may not be needed. CT is the most sensitive investigation for detecting renal and ureteral calculi.

Excretory urography / Computed tomography / Intravenous pyelogram

Urography is imaging with and without contrast material to evaluate or detect pathology in the urinary tract. Intravenous pyelogram (IVP) is urography with a conventional x-ray. It can also be performed using computed tomography (CT) or magnetic resonance imaging (MRI). Excretory urography is a contrast study for verifying and localizing upper urinary tract disease.

Excretory urogram has been replaced by CT scan. First it is done without any contrast. This is followed with intravenous contrast and with a delayed plain KUB X-ray. As the contrast increases risk of nephropathy, it is contraindicated in patients with deranged kidney function(15).

Creatinine clearance time

Rrenal function is assessed with creatinine clearance time. It is considered to be gold standard test. It also approximates the glomerular filtration rate(GFR) (15). Its accuracy depends on meticulous urine collection. Spinal cord injury patients have reduced muscle mass, as a result it may give inaccurate report.

Isotope studies

Evaluation of functional area of renal cortex is done by Technetium-99m dimercaptosuccinic acid (DMSA) scan (28).

Technetium-99m mertiatide (MAG-3) renogram is done for evaluation of urinary tract drainage and assessment of its differential function. In patients with suspected ureteral reflex the bladder is drained with an indwelling catheter prior to these tests (29).

Lower urinary tract tests:

Urine analysis , Urine culture and sensitivity testing

It is done for almost all patients with neurogenic bladder. It can be repeated as necessary. It should be done in following cases:

1) in cases of symptomatic urinary tract infection
2) appearance of any new symptoms of infection.
3) before any invasive procedures

New symptoms can be increased leaks, frequency, etc. Bacteriuria should be treated prior to any invasive urologic procedure(15).

Post void residual urine (PVR)

It is a simple tool for assessment of lower urinary tract symptoms . The quality of voiding is determined by the volume of urine remaining in the bladder after voiding (17). A balanced bladder has PVR of less than 20% of bladder capacity. High intravesical pressure can be present despite low PVR. PVR can be determined by inserting catheter or US. It is clinically useful after comparing with previous recordings. It has to be done in conjunction with bladder pressure, clinical symptoms and appearance of the bladder wall. PVR can vary in different time of day and season(15).

Cystography

It is done to know about vesicoureteric reflux.

There are 3 types of cystography :

(1) retrograde cystography

(2) voiding cystourethrography

(3) radionuclide cystography(30).

Cystography shows the bladder outline and shape. The video-urodynamic study, including fluoroscopy of the bladder and intravesical pressure, are useful tools in some cases.

Cystoscopy

There is increased risk for changes in the bladder mucosa of patients who are on long term indwelling urethral or suprapubic catheterization. Although rare but it is a risk factor for development of tumour. Risk of tumour development is is about 0.39% in persons with SCI(31). Cystoscopy is recommended after five years in high-risk patients, such as smokers. It should be done after ten years if there are no risk factors. Recurrent lower urinary tract infections are an indication for a cystoscopy to rule out bladder calculi and the presence of foreign bodies like hairs, which can be introduced by catheterization(15).

Cystometrography (CMG)

Cystometrography is a dynamic study of bladder filling and voiding. Normal saline is the most commonly used filling agent. Carbon dioxide (CO2) can also be used as the filling agent. This method of testing has shown poor reproducibility, considerable variation and presence of artefacts(32). For water CMGs,two-channel catheters are used. One channel fills bladder and the other records vesical pressure. A rectal pressure trace helps in distinguishing intravesical pressure variations resulting from intra-abdominal transmission from detrusor contractions. Filling rates can vary from 6 ml to 100 ml per minute. Filling rate less than the predicted maximum filling rate is called physiological filling rate. The predicted maximum filling rate as ml/min is obtained by dividing maximum body weight in Kg by 4. Filling rate more than the predicted maximum filling rate is non physiological filling rate(26). Patients are asked to suppress voiding during filling phase. Normal bladder capacity ranges from 300-600 ml. The initial filling

sensation occurs approximately at 50% of the bladder capacity. In Non SCI patients the sensation of normal fullness is perceived in the lower abdomen, while a sense of urgency in the perineum. Howver these sensations can be absent in SCI patienst. The change in volume divided by the increase in baseline pressure during filling phase determines bladder's compliance. Compliance is determined in the absence of a detrusor contraction. It should be greater than 10 ml/cm H20 for normal compliance. 10-20 ml/cm H20 is considered as borderline if the bladder capacity is reduced. Any involuntary detrusor contraction during the test is an appreciable phasic pressure change. It is considered abnormal. These contractions are referred to as detrusor overactivity if the patient is neurologically intact. In patients with suprasacral or supraspinal lesion these contractions are called as neurogenic detrusor overactivity.

Patients with a neurogenic bladder are instructed to void at capacity, but many may not be able to generate a detrusor contraction. The presence of involuntary detrusor contraction confirms the presence of detrusor hyperactivity. It is commonly seen in a patient with suprasacral or supraspinal lesion. In a patient with infrasacral lesion absence of the detrusor contraction is not necessarily an indication of bladder areflexia. CMG can be used to confirm the return of detrusor reflex in spinal shock phase. It can be done before starting pharmacotherapy for detrusor hyperactivity in patients with supraspinal or suprasacral lesion(15).

Urethral pressure profiles

Urethral pressure profiles are measure centrally acting forces by gradually withdrawing a measuring device. Measuring devices used are a micro tip transducer or perfused side-hole catheter. It helps in determining presence of sphincter-active area after sphincterotomy.

Sphincter electromyography

It is done along with CMG or video-urodynamic study. Needle and surface electrodes are placed over the levator muscle, perianal or periurethral muscles for recording EMG(31). The bladder pressure and integrated EMG recordings are displayed simultaneously. Increase in EMG activity is noticed when the bladder capacity reaches a maximum during filling phase. It becomes unresponsive just before voiding. Incomplete spinal cord injury, low levels of EMG activity can be seen during the filling phase. The EMG activity in the sphincter might increase rather than decreasing in reflex detrusor contractions. In detrusor-sphincter dyssynergia (DSD), voiding occurs at the end of detrusor contraction because the striated sphincter relaxes more quickly than the smooth muscle of the bladder. Denervation can be diagnosed with a standard needle EMG.

Video urodynamics

Video urodynamics is used for dynamic activities of lower urinary tract. It helps to know about the filling and voiding phases. It is indicated in patients who have incontinence with sense of incomplete voiding. It can be used for diagnosing mechanical obstruction

and neuropathy. It detects detrusor sphincter dyssynergia. It is also useful to assess detrusor contraction and the presence or absence of bladder neck obstruction. It is a study like CMG where a two-channel catheter placed in the bladder and a balloon catheter in the rectum. Sphincter EMG are recorded along with the bladder, rectal and detrusor pressures. Detrusor pressure is calculated as difference of rectal and vesical pressure. The bladder is filled with contrast solution.. The bladder image are monitored intermittently by fluoroscopy and the radiographic and urodynamic image is mixed on the same screen. Recordings are videotaped. After the patient sit and void , flow rate is calculated(15).

Uroflowmetry

It is used to know the flow rate of the external urinary stream. Flow rate is measured as volume per unit time in millilitres per second (ml/s). Uroflowmetry is a non invasive and cheap procedure. It is a screening test for patients with lower urinary tract symptoms and able to void(33).

Urodynamic measurement gives an objective and qualitative information about the storage and voiding symptoms. Adequate privacy is provided to facilitate voiding as per his/her ‘‘normal’’ desire to void. Automated data analysis should be verified, and artefacts removed. It should be cross checked with the patients whether their voiding was representative of their usual pattern. Uroflowmetry results are compared with the data in the bladder diary. After estimation of post-void residual volume the non-invasive assessment of mechanical obstruction and voiding function is complete(34).

Management of neurogenic bladder

The main objective of neurogenic bladder management is maintaining social continence. It is done by promoting storage of urine and facilitating bladder emptying(21). Management includes lifestyle modification, pharmacological and surgical interventions. The standard line of management in neurogenic bladder includes reducing detrusor overactivity and promoting bladder emptying. Bladder emptying is done by clean intermittent catheterization(CIC). It improves quality of life and facilitates rehabilitation(35).

Behavioral management

Timed voiding

Timed voiding is taught to patients with overactive bladder leading to urgency or reflex incontinence. Patients are trained to urinate prior to the anticipated detrusor contraction. It is more beneficial for patients with sphincter weakness, because the incontinence worsens when the bladder is full. Fluid intake should be balanced along with timed voiding to maintain continence.

Bladder stimulation

Bladder stimulation can be done by stroking or pinching the perineal skin. It causes reflex simulation. It has limited effectiveness. Suprapubic tapping causes the mechanical stretch of the bladder wall. Stretching of bladder wall subsequently leads to bladder contraction.

Deeper indentation of the bladder with a jabbing technique is effective technique in limited population. Paraplegic patients who have good upper limb function can use it on condom catheter(36).

Valsalva and Credè's manoeuvre

Patients with areflexic bladder can use straining or valsalva manoeuvre. Emptying by straining is possible for flaccid pelvic floor muscles. Credè's manoeuvre helps in mechanically pushing the urine out of the bladder. It is done in a relaxed abdominal wall. In long term Crede's manoeuvre has been reported to be superior than continuous bladder catheterization(37).

Anal stretch voiding

Anal stretch voiding is done by emptying the bladder by relaxing the pelvic floor. Pelvic floor relaxes by stretching the anal sphincter and the Valsalva manoeuvre. Anal stretch technique is used as effective voiding in paraplegic people with the spastic pelvic floor(15).

Urine collection devices

External condom catheter is the best tool for urine collection in tetraplegic patients, because they are unable to perform self-catheterization. Outflow obstruction if any should be adequately treated prior to using collection devices. Poor perineal hygiene can lead to recurrent UTIs. Tight application of condom can lead to skin break down.

There are two types of indwelling catheters:

(1) urethral

(2) suprapubic.

Indwelling catheters are used after failure of all other measures or for patient's convenience. Patients are advised regular catheter change, adequate fluids intake, controlled movements. Special instructions are given to avoid traction on the catheter. Traction of the catheter leads to urethral injury in SCI patients. Frequency of catheter change depends on type of catheter and risk of UTI.

Clean Intermittent Catheterization (CIC):

Since Greek times it has been reported that disorders of bladder filling or emptying, lead to urinary tract infection. UTI due to neurogenic bladder was a major cause of morbidity and mortality in spinal cord injury patients till clean intermittent catheterization was routinely used. Around 1880, CIC was first described in England to a Syphilis patients with bladder dysfunction. Sterile intermittent catheterization for acute spinal cord injury patients was first reported by Guttmann and colleagues. All catheterizations on male patients were done by physician. Doctor was assisted by a nurse. Female catheterization was done by registered nurses. The non-touch technique was practiced and done with full aseptic precautions. This practice resulted in reduced urinary tract infections(38).

In 1970, Lapides and colleagues treated a women with Multiple sclerosis and neurogenic bladder. She had history of multiple UTIs. Her social and sexual life was severely

jeopardized due to the urinary incontinence. Lapides and team developed “clean intermittent catheterisation” technique. In this catheter was only cleaned with an antiseptic solution and the patient did catheterization after washing her hands only. There was no use of sterile gloves or forceps nor sterilization required.(39).

It was hypothesized that host resistance factors would check symptomatic urinary tract infection if clean intermittent catheterization was done properly. Also bladder has to be emptied regularly to avoid overstretching(39).

Patient was trained for clean intermittent catheterization. The patient washed her hands with soap and water. She had to assume a lithotomy position on the table, with her feet on the table and the knees held apart to expose the urethral meatus and introitus. A hand mirror was placed at the foot end of the table so that the she could visualize the urethral meatus when it was pointed out to her by the nurse. A catheter with some lubricant on the tip was given to her. She had to insert the catheter through the urethral meatus into the bladder. Once she had drained the urine, she had to remove the catheter slowly. She was advised to do clean catheterization every few hours to maintain continence. It was reported by the patient that once her catheter fell on the toilet floor. At that time she did not have any antiseptic solution to sterilize it. And she continued with catheterization and did not develop any complication. This showed insignificance of sterility for catheter care. These finding revolutionized the management of urinary incontinence and since then CIC remains the mainstay treatment of neurogenic bladder management (39).

Types of clean intermittent catheterization:

1. **Clean Intermittent Self Catheterization**: Patient himself does intermittent catheterization at regular intervals.

2. **Attendant Intermittent Catheterization:** Caregiver does the catheterization intermittently. It is done in those patient whose hand function is compromised.

3. **Sterile Intermittent Catheterization:** Performed by medical personnel in aseptic condition. It is done in acute or emergency conditions only.

CIC can be started in any age group. Children as young as five years can do CIC(38). Patient's caretaker can be trained attendant CIC as an alternative. Attendant CIC is socially unacceptable in most cases. Important pre-requisites to initiate CIC is proper patient selection and willingness from the patient to learn.

Main advantages of CIC are:

1. It reduces risk and incidence of UTIs

2. Reduction in incidence of renal and bladder calculi

3. Patient is continent between catheterizations and participates in social activities

4. Increased satisfaction in sexual life in the patients and their partners due to freedom from continuous catheterization (40).

In terms of urological complications Clean intermittent catheterization is the safest bladder management method for SCI patients. Selection of a bladder management method affects quality of life(41).

Pharmacological management

Drugs inhibiting detrusor overactivity are the most useful and effective on persons with neurogenic bladder.

Anticholinergic drugs

It is used to decrease detrusor overactivity. Propantheline bromide and Hyoscyamine and oxybutynine can be used. Oxybutynin is most commonly used among anticholinergic drugs. For adults starting dose is 5mg once daily. Dose can be increased to four times a day. Patients with hepatic impairments require dose adjustment. Oxybutynin solution can also be directly instilled inside the bladder. Dry mouth and constipation are the common side effects of anticholinergic drugs. Oral administration has been reported to have lesser side effect compared to other parenteral mode(42). Transdermal patch of oxybutinin are also available, but skin irritation limits its use. Tolterodine, a muscarinic receptor antagonistcan be used in patients who have severe renal or hepatic impairment . It's doses range from 1 mg to 2 mg twice daily. Oxybutinin and Darifenacin are available as an extended-release tablet. Darifenacin bind to M3 receptors at doses ranging from 7.5 mg – 15 mg. Trospium, another anticholinergic is given at a dose of 20 mg twice daily or as a sustained-release preparation at 60 mg once daily. Dry mouth, blurry vision and

constipation are common side effects(43). Severe side effect on long term use is one of the reasons for poor compliance on long term use.

Adrenergic antagonists

It acts by increasing emptying in neurogenic voiding dysfunction. It includes **α**1adrenergic receptor antagonists.Common drugs in use are Terazosin, prazosin, and doxazosin. Tamsulosin is commonly used adrenergic antagonists and it has fewer vascular effects including hypotension(44). It acts by relaxing muscles in the prostrate and bladder neck, leading to ease in urination. These agents are also effective in managing the vascular manifestations of autonomics dysreflexia.

Adrenergic agonists

It acts by increasing urethral resistance. It is more useful in patients with mild stress incontinence. Serotonin and norepinephrine reuptake inhibitors like Duloxetine can be used to prolong the **α**-adrenergic effects on the external urethral sphincter(45).

Estrogens

Post-menopausal women can have stress incontinence due to atrophy of urethral sub-mucosa. Estrogen application can be done in those cases. It helps in incontinence by restoring or maintaining the tissue(46).

Muscle relaxants

Antispastic medications like tizanidine, baclofen and dantrolene sodium are common muscle relaxants in use. Their efficacy in reducing detrusor sphincter dyssynergia is doubtful. Intrathecal baclofen has been observed to depresses the pelvic floor reflexes as well as the detrusor reflex. Its role in managing an overactive bladder is limited.

Intravesical therapy

For decreasing bladder hyperactivity Botulinum A toxins can be used. It is injected at 30-40 sites in the bladder wall musculature. Maximum of 200 units can be given at a time. It reduces detrusor overactivity for up to 4- 6 months. The injection can be repeated after six months(47).

Resin fear toxin has been used for intravesical injections. It has shown improvement in symptoms of the overactive bladder(48).

Surgical Management

Surgical management of neurogenic bladder includes bladder augmentation, continent diversion and denervation procedure.

1. Bladder augmentation: It is advised to patients with detrusor hyperactivity. It can also be done in patients with reduced compliance due to failure of response to anticholinergic drugs. The main aim is to create a low-pressure reservoir. The patient need regular CIC even after the surgery. Malabsorption syndrome, decreased intestinal

transit time, chronic bacteriuria, possible risk of neoplastic change are possible long term complications. It has been reported to have a high level of patient satisfaction(49).

2. Continent diversion: It is technique to open continent catheterize channel into the abdominal wall. A section of the bowel is used to increase bladder capacity. It is indiacted in patients with false passages or fistulas, or those who are unable to do CIC because of strictures(50). The appendix, intussuscepted small bowel, dysfunctional segment of the ureter and terminal ileum with the ileocecal valve are used for surgery. It may require closure if there is sphincter related incontinence.

3. Denervation procedure: Denervation procedure is done by interrupting the peripheral nerve supply near the bladder or sectioning the sacral nerve roots. The detrusor reflex is mediated by S3 nerve root. In selective sacral rhizotomy, S3 nerve root is identified and is denervated(51). It leads to temporary areflexia. Iit has been observed that over time, detrusor reflex can reroutes through the other intact sacral roots. Sacral reflex are abolished permanently by bilateral S2, S3 and S4 denervation. It can abolishes reflex erections and also lead to worsening of bowel incontinence. Peripheral denervation of the detrusor can be done by transecting the detrusor above the trigone area of the bladder followed by resuturing. This results in denervation of paravesical ganglia. Other method is by over distending the bladder. Over distension damages intramural nerves and muscles(52).

Alternative approaches in Bladder Management

Electrical stimulation

The detrusor contraction can be modulated byelectrical stimulation. In this electrodes are implanted on the pelvic nerves, bladder wall, sacral roots and the conus. The electrodes can also implanted in the anterior roots. Anterior root implantation can be either intradural or extradural. Spontaneous hyperactive contractions can be prevented by bilateral S2, S3, and S4 dorsal rhizotomies. Modification of the stimulus parameters and electrode design by super selective rhizotomies, are under trials(53). Procedures to increase bladder outlet resistance can be done. In patients with incontinence from decreased outlet resistance, urethral compression can be tried. It include injection therapy into the bladder neck and urethra, due to which there is increase in bulk of the tissue under and around the bladder neck. It leads to formation of fascial sling or an artificial sphincter(54).

Injection therapy

Since years stress incontinence are managed by Teflon injections in the urethra. Risk of particle migration discourages its use(55).

External compressive procedures

Surgical management for stress incontinence includes fascial sling procedures. Low pressure and compliant bladder is prerequisite for this procedure. Sling is made from

patient's own abdominal wall. 2-3 cm strip of fascia are taken from the anterior rectus abdominal fascia. Tensor fascia lata can also be used for taking fascia. Then strip of one side is attached to abdominal fascia or pubic tubercle and other side it encloses the bladder neck. After this procedure lifelong CIC will be needed and it will be difficult to void with Valsalva or Crede methods.

An artificial urethral sphincter is used to treat moderate to severe stress urinary incontinence. It consist of a cuff, a control pump and a pressure-regulating balloon. The cuff is implanted around the neck of urinary bladder. The pump is implanted in the labia or scrotum. This allow the patient to open the cuff during voiding. It is more effective in male compared to female. Valsalva manoeuvre is used and CIC may not be needed after this procedure. Artificial sphincters makes a significant impact on patients quality of life(56).

Procedures for management of outlet resistance

Sphincterotomy procedures are mainly done in male patients. It is indiacted in those patients who are cannot do clean intermittent catheterization. In such patients Condom catheters are ideal urine collection devices. The striated sphincter are usually ablated by incision. In older patients with prostatic obstruction, resection of prostrate may be needed. Recurrent obstruction by stricture formation or dyssynergia adversely affect long term outcome(57).

UTI is most common complication of all the above mentioned methods for management of neurogenic bladder.

Management of Urinary tract infection (UTI)

Recurrent UTI is common in patients with neurogenic bladder. Incidence of bacteriuria with fever is more in patients who followed attendant assisted catheterization than in patients on indwelling catheters or self clean intermittent catheterization (58).

The role of prophylactic antibiotics for UTIs in SCI patients on CIC has been studied extensively. In a randomized control trial the possible role of trimethoprim-sulfamethoxazole prophylaxis in the first four months of CIC was studied. It was done during bladder training of SCI patients. It was observed that men in antibiotic group had significant reduction in bacteriuria and symptomatic UTI compared to those on placebo. Adverse events related to antibiotic treatment and the emergence of drug resistance are common. This limits the usefulness of antibiotics for prophylactic management of UTIs.

It has been observed prophylactic antibiotics significantly reduced bacteriuria but not clinical UTIs during initial management with CIC(59). Benefits and adverse effects of antimicrobial prophylaxis has to be balanced for UTI in patients with SCI(60).

Few studies has raised doubts to use of prophylactic antibiotics during CIC. One study has reported two-fold increase in number of antimicrobial-resistant bacteria when antibiotics were used for prophylaxis(61).

Drug resistance can be reduced by balanced use of antibiotics. Repeated exposure to antibiotics due to recurrent UTIs is common in spinal cord injury patients doing CIC. It is responsible for increased incidence of multidrug-resistant bacteria.

New onset of UTI symptoms with urine analysis suggestive of bacteriuria, leukocyturia and positive urine culture are characteristic of catheter associated UTI.

The symptoms of UTI include: -

- Fever: Temperature above normal body temperature(> 38 C). In the presence of a fever, signs of sepsis should be checked. Poikilothermia should be ruled out in patients with cervical and high thoracic lesions.
- Urinary incontinence
- Leaks around the catheter
- Increased spasticity
- Tiredness
- Cloudy urine with or without presence of mucus or sediment.
- Foul smelling urine or a distinct change in urine odour
- Pyuria/leukocyturia: presence of white blood cells on urinalysis.
- Symptoms such as headache, sweating, flushing due to noxious stimuli like bladder distension/bladder infection(62).

Excessive treatment with antibiotics can lead to the development of multi-resistant organisms. Therefore cautious and judicious use of antibiotics is advised.

Justification for the current study

Spinal cord injury is an ailment that directly or indirectly affects all body system. One of the most distressing complaints for patients with Spinal cord injury (SCI) is urinary dysfunction. In SCI patients, the loss of supra spinal control can be responsible for over activity of detrusor muscles, leading to small bladder capacity. As a result of which patient may have high bladder pressure, vesicoureteral reflux and renal impairment. Intermittent clean catheterization along with antimuscarinic drugs is gold standard for management of spinal cord injury with neurogenic bladder. Long term use of antimuscarinic drugs has its own side effects like dryness of mucosa, blurring of vision etc. Sacral neuromodulation , tibial nerve stimulation, and pudendal nerve stimulation are considered very valuable for the management of neurogenic bladder secondary to SCI; but, because of invasive nature, it has its own limitations. It has been found that stimulation of the somatic afferent pathways can be an important factor in the efficacy of neuromodulation. Results of the study conducted earlier in our department showed improvement in leaks as per voiding chart after two weeks of stimulation of posterior tibial nerve. In our study we tried to find if surface electrical stimulation of tibial nerve branch i.e medial plantar nerve at sole of foot can help in modulating spinal reflex pathways for reducing detrusor over activity.

Methodology

Setting

The present study was conducted at the Department of Physical Medicine and Rehabilitation (PMR), Christian Medical College (CMC), Vellore, Tamil Nadu, India. Christian Medical College Vellore is a 3000 bedded tertiary care hospital. It has average outpatient census of about 5000 patients per day. The Department of PMR, CMC rehabilitates approximately 120 inpatients and 100 outpatients are rehabilitated per day. Approximately, 400-600 patients with SCI are rehabilitated per year. The patients requiring long-term rehabilitation program are admitted in Rehabilitation Institute, Department of PMR, CMC Vellore.

The study

This prospective interventional study was approved by the Institutional Review Board and ethics committee (Ref no. 11061/20.12.2017), Christian Medical College. Twenty patients fulfilling the inclusion criteria were recruited in the study. Informed consent was obtained prior to the commencement of clinical trials. Basic demographic details including name, age, sex, address, socio-economic background, level of the injury, cause of injury, medical history were recorded from the patient and medical charts.

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Standard of Care Practice

At Department of Physical Medicine and Rehabilitation, Christian Medical College Vellore, Tamil Nadu, India patients with neurogenic bladder are advised to do four hourly clean intermittent catheterization (CIC). Routine urine sample culture and sensitivity investigations are done prior to the start of bladder management to rule out the possibility of urinary tract infection (UTI). Medical management such as antibiotics are planned based on the results of urine culture and sensitivity otherwise patient is treated symptomatically. Patient's urinary bladder as well as upper urinary tract screening is done through diagnostic Ultrasonography (US) procedure. This investigation helps to rule out conditions such as hydronephrosis and renal or bladder calculi. For the patient with possibility of calculi, as diagnosed by US, further investigations such as Kidney, ureter and bladder (KUB) X-ray and in some cases cystoscopy (only for bladder calculi) are done. The Cystometrogram (CMG) procedure is also performed to obtain pressure volume relationship as well as to obtain type of bladder. The anticholinergic drugs such as Oxybutynin, Tropan, Tolteroidine etc. are prescribed to the patients with detrusor overactivity whereas patients with open bladder condition are treated with tablet such as Amitriptyline.

Proposed Research Methodology

Patient having urinary incontinence and symptoms of detrusor overactivity, were invited to try out the electrical stimulation of sole of the foot. Patients were asked to withdraw

drugs pertaining to treatment of detrusor overactivity (if any) and were also asked to maintain voiding chart one week prior to the treatment. The format of voiding chart had clock type picture (Figure 4) for filling volume of fluid intake, urine output and record of any leaks at a given time. Patient meeting the inclusion/ exclusion criteria were asked to continue maintaining voiding chart as well as were instructed to continue 4 hourly CIC during the study period.

Following inclusion/exclusion criteria were used for the study:-

Inclusion criteria:

1. Patient with spinal cord injury having at least one leak per day as reported in the voiding chart.
2. CMG proven detrusor overactivity
3. On Clean Intermittent Catheterization
4. Presence of Ankle jerk
5. Age-18 years and above.

Exclusion criteria:

1. Peripheral neuropathy
2. Urinary tract infection
3. Pregnant women
4. Any psychiatric ailment
5. Symptoms of stress urinary incontinence

6. Presence of any implantable devices such as pacemaker, cochlear implant or any metallic implantable plate were contraindication for this study.

Cystometrogram was performed using Life-Tech UroLab machine, Life-Tech Inc., Houston, TX, USA (Software: opus version 1.71) on days 1 and 15 of the study period. Integrity of the tibial nerve spinal reflex loop arc was confirmed by presence of ankle jerk. Stimulation was given by using a custom made nerve stimulator developed at Rehab Research Laboratory, Department of PMR, CMC Vellore. The parameters of the stimulator were kept same as our previous study (Ojha et al; Ojha PhD thesis2013)(1,63)) i.e. 200 μs pulse width, rectangular pulses with current strength ranging between 10–80 mA and frequency 20 Hz. Self- adhesive Pad (Size: 9x5cm/3.5x2inch, Segolike ASIN : B072PV3GTC) electrodes were used for stimulation. Cathode was placed on the medial planter nerve, a branch of tibial nerve i.e. at the level of medial arch of foot while anode was placed approximately 2cm apart at the level of metatarsophalangeal (MTP) joint(Figure 3). The electrodes were customized to fit the site of stimulation for each patient. Stimulation was given for 30 minutes per session each day for 14 consecutive days.

Figure 3. Placement of electrodes

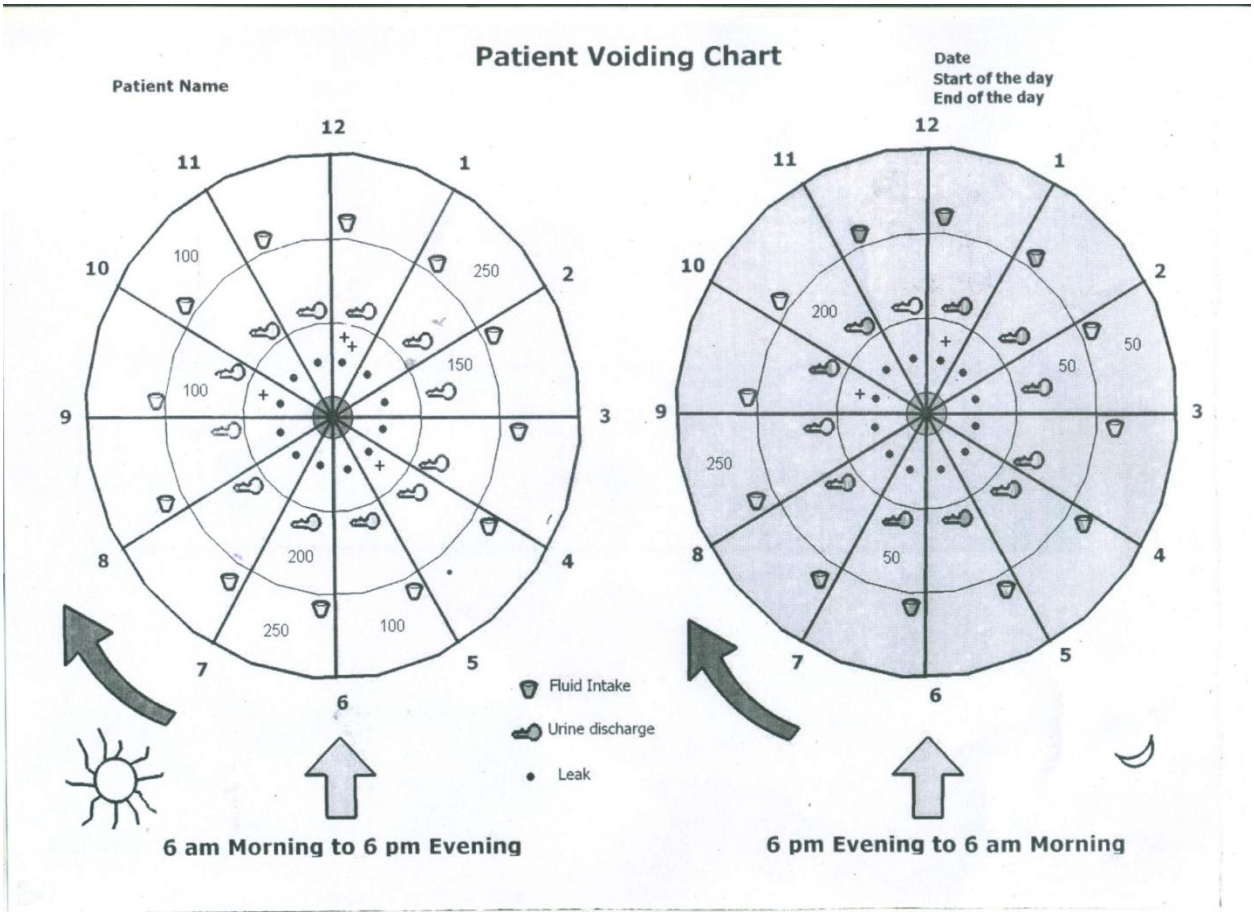

Figure 4 . Patient voiding chart

Analysis of Data from Voiding Chart

The parameters obtained from the voiding diary were categorized into five categories for analysis:-

1. Amount of fluid intake per day
2. Total volume of urine voided per day,
3. Frequency of leaks,
4. Frequency of CIC

5. Maximum volume of urine output in a day

A comprehensive voiding chart analysis score (Cumulative Voiding Chart Index) was conceptualized from the trend lines of the parameters obtained from voiding chart between day -7 to day 14.

Rational and Method of Cumulative Voiding Chart Index (C*v*C*i)*

Though the voiding chart/ bladder voiding diary is clinically/ socially useful tool routinely used by the medical professionals and care givers for reporting the day to day state of fluid intake and output. However, there is no index/tool/ scoring system exists which gives comprehensive score which gives overall state of the bladder state through voiding chart. Hence, it was decided to come-up with the novel tool which can quantify the comparative state of the bladder from the voiding diary.

Each voiding chart parameter was graded either -1 (worsen), 0 (no change) or +1 (improved) as a representation of state of the bladder (pre and post-intervention) in Cumulative Voiding Chart Index (C*v*C*i*). Trend in reduction in number of leaks, increase in amount of fluid intake, increase in urine output and increase in maximum volume of urine voided in a day was considered as an improvement and was scored as +1. Patient with no significant visible trend in these parameters was scored as 0 representing no change while increase in trend in number of leaks, decrease in amount of fluid intake, decrease in urine output and decrease in maximum volume of urine voided in a day was considered as deteriorated state in bladder and was scored as -1. The nominal number of

CIC advised per day is 6 assuming 4 hourly CIC. The trend in decrease in CIC leading to the nominal prescribed value was considered as improvement (score +1) while increase in CIC was considered as worsen bladder state (score -1). Person maintaining same number of CIC pre and post-intervention was graded as 0 for no change in frequency. Of the five categories a person can have cumulative score ranging from -5 to +5 (-5 representing poor, +5 representing good) i.e. higher the score better the state of bladder.

Voiding chart data for the patient developing UTI during the study period was excluded for the days which he/she was treated for UTI management clinically without change in stimulation protocol. However, additional stimulation was given to compensate for the days. Binomial distribution test with test proportion of 50% was used as a statistical test to determine p-value amount the improved population against not improved population.

Analysis of Data from Cystometrogram

Pre and post reflex volume, cystometric capacity and maximum detrusor pressure obtained from CMG procedure were analyzed. The volume at which the first onset of detrusor contraction was considered as reflex volume. The volume at which a first leak occurs during urodynamics procedure or the volume at which patient felt discomfort or maximum volume infused whichever is earlier was considered as cystometric capacity (Ojha et. al)(1).

The highest detrusor pressure recorded from the CMG was considered as maximum detrusor pressure. Percentage change from the initial state was determined for each patient (equation 1).

$$(Post - Pre)\ x\ 100\ /Pre \qquad \text{- (1)}$$

Percentage change (> 10%) from the initial state of bladder was considered as an improvement while percentage change (< -10%) was considered as deteriorated state of the bladder. The intermediate percentage between -10% to +10% was considered as no improvement.

The Wilcoxon signed rank test was used for statistical analysis on pre- and post-intervention data available from CMG recording (i.e. reflex volume, maximum pressure and cystometric capacity). The p-value < 0.05 was considered significant at 95% confidence interval.

Feedback Questionnaire

The subjects were asked to fill satisfaction of life questionnaire at the end of the treatment (i.e. Day 14).

At the end of the study period, the bladder was managed as per the standard treatment protocol.

The overall flow chart of the study is shown in Figure 5.

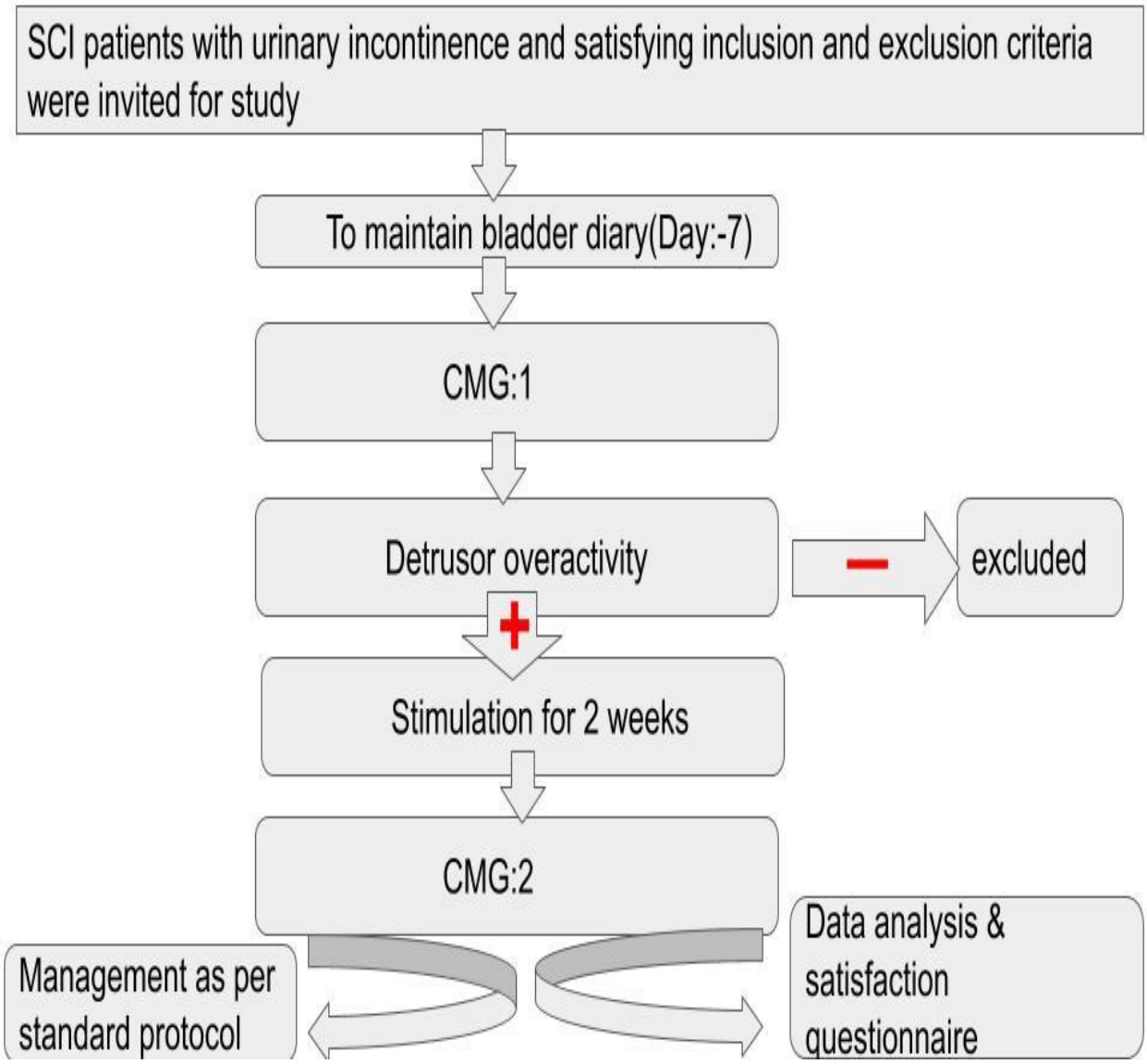

Figure 5. Flow chart of the study

Results

In this pilot study, 20 patients with SCI met the key inclusion/exclusion criteria. Subjects had either traumatic or non-traumatic etiology. The basic demographic details of the 20 participants is shown in Table 2.

Of the 20 participants, 17 were male and 3 female. Ten had complete and rest had incomplete spinal cord lesion. The mean age of the participants were 36 years and the time since injury ranged from 9 to 132 months. The neurological level of the participants ranged from C6–T3 (3 subjects), T4–T10 (16 subjects) and T11–L3 (1 subjects). Table 2 also shows that 12 subjects had traumatic spinal cord injury with ASIA grades grade A (9 subjects), grade B (2 subjects), and grade C (1 subject).

Following treatment, 12 subjects showed increase, 6 showed decrease and 2 had no significant change in reflex volume as defined by 10% improvement criteria reported in methodology section. Thirteen patients had reduction, 3 had increase and 4 had no significant change in maximum pressure from the baseline. There was significant improvement in cystometric capacity of 14 subjects, 3 did not show much improvement and remaining persons showed reduced bladder capacity. The mean and standard deviation for change in reflex volume was 45.75 ± 88.71 ml (mean ± sd), maximum pressure was −12.49 ± 35.69 cm of water and cystometric capacity was 69.88 ± 104.64 ml (Table 3). The p-value as determined using Wilcoxon signed ranked test for change in

Table 2. Demographic characteristics of the study population

(I=Incomplete, C= Complete, N= Non-traumatic, T=Traumatic, M=Male, F=Female)

Subject	Age	Duration of injury (month)	Level of injury	Type of Injury	Cause of Injury	ASIA Grade	Sex
S1	45	18	T5	I	N	-	F
S2	47	12	L3	I	N	-	M
S3	46	99	T5	C	T	ASIA-A	M
S4	28	9	T5	C	T	ASIA-A	M
S5	37	60	T5	C	T	ASIA-A	M
S6	26	15	T7	I	N	-	M
S7	36	18	T4	C	T	ASIA-A	M
S8	27	54	T5	C	T	ASIA-A	M
S9	25	80	T6	C	T	ASIA-A	M
S10	34	42	T4	I	T	ASIA-B	M
S11	28	42	C5	I	N	-	F
S12	24	12	T4	C	T	ASIA-A	M
S13	47	48	T10	I	T	ASIA-B	M
S14	44	36	T8	I	N	-	M
S15	59	21	T9	C	T	ASIA-A	M
S16	27	12	C5	I	T	ASIA-C	M
S17	23	30	T4	C	N	-	F
S18	56	120	T5	C	T	ASIA-A	M
S19	22	29	T8	I	N	-	M
S20	41	132	C8	I	N	-	M
Median	**35**	**33**		**I = 10**	**T=12**	**ASIA-A = 9**	**F=3**
Min	**22**	**9**		**C = 10**	**N=8**	**ASIA-B =2**	**M=17**
Max	**59**	**132**				**ASIA-C =1**	

cystometric capacity (p-value=0.04) and detrusor pressure (p-value=0.03) were found to be significant and there was no significant change in reflex volume (p-value= 0.13).

Table 3. Pre and Post CMG data

	Reflex Volume			Max Detrusor Pressure			Cystometric Capacity		
Subject	**Pre**	**Post**	**% change**	**Pre**	**Post**	**%Change**	**Pre**	**Post**	**%Change**
S1	202	171	-15.3	34	31	-8.8	205	177	-13.7
S2	342	275	-19.6	53	48	-9.4	397	357	-10.1
S3	206	347	68.4	64	88	37.5	265	820	209.4
S4	136	176	29.4	94	73	-22.3	152	273	79.6
S5	117	200	70.9	26	19	-26.9	117	207	76.9
S6	47	69	46.8	109	82	-24.8	53	97	83.0
S7	125	404	223.2	162	86	-46.9	128	439	243.0
S8	230	347	50.9	73	76	4.1	381	500	31.2
S9	168	221	31.5	56	41	-26.8	169	246	45.6
S10	340	337	-0.9	100	82	-18.0	343	355	3.5
S11	24	33	37.5	91	42	-53.8	24	47	95.8
S12	296	165	-44.3	53	47	-11.3	354	169	-52.3
S13	152	122	-19.7	101	87	-13.9	163	147	-9.8
S14	180	120	-33.3	44	84	90.9	270	171	-36.7
S15	196	143	-27.0	90	69	-23.3	200	196	-2.0
S16	130	219	68.5	61	58	-4.9	130	219	68.5
S17	64	84	31.3	77	49	-36.4	68	85	25.0
S18	76	83	9.2	93	132	41.9	81	83	2.5
S19	30	128	326.7	158	49	-69.0	30	130	333.3
S20	157	284	80.9	47	34	-27.7	157	510	224.8
Mean	**160.9**	**196.4**	**45.75**	**79.3**	**63.85**	**-12.49**	**184.35**	**261.4**	**69.88**
Std. Dev	**92.79**	**105.77**	**88.71**	**36.41**	**26.72**	**35.69**	**116.19**	**189.14**	**104.64**
Std. Err	**20.75**	**23.65**	**19.87**	**8.14**	**5.98**	**7.98**	**25.98**	**42.29**	**23.40**
	Improved 12			Improved 13			Improved 14		
	Worsen 6			Worsen 3			Worsen 3		
	Not improved 2			Not improved 4			Not improved 3		

The figure 6 shows trend in voiding diary data and C*v*C*i* score of a subject who had noticeable improvement in frequency of leaks (6a), total fluid intake (6b), total urine output (6c), maximum urine output of the day (6d) keeping number of CIC (6e) same

with two weeks of stimulation. The frequency of ICC decreased in 3 patients. One subject had UTI during treatment period who was treated with urine culture-specific antibiotics. The stimulation period was extended for a week in that subject.

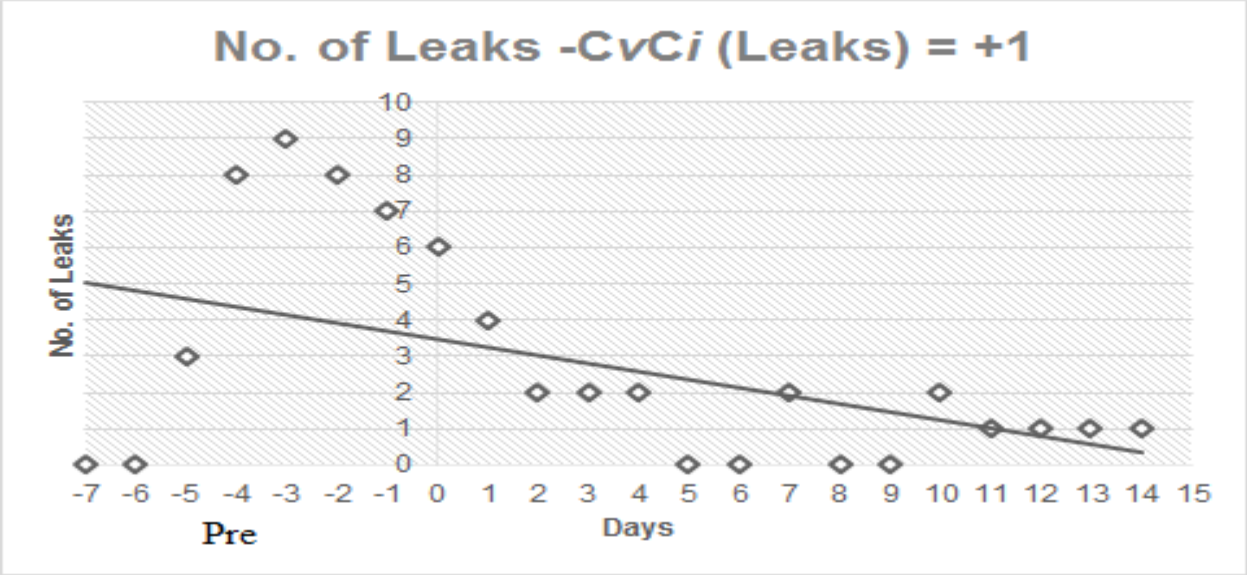

Figure 6a. Trend in Number of Leaks Pre-Post Stimulation of a S16 with C*v*C*i* (+1)

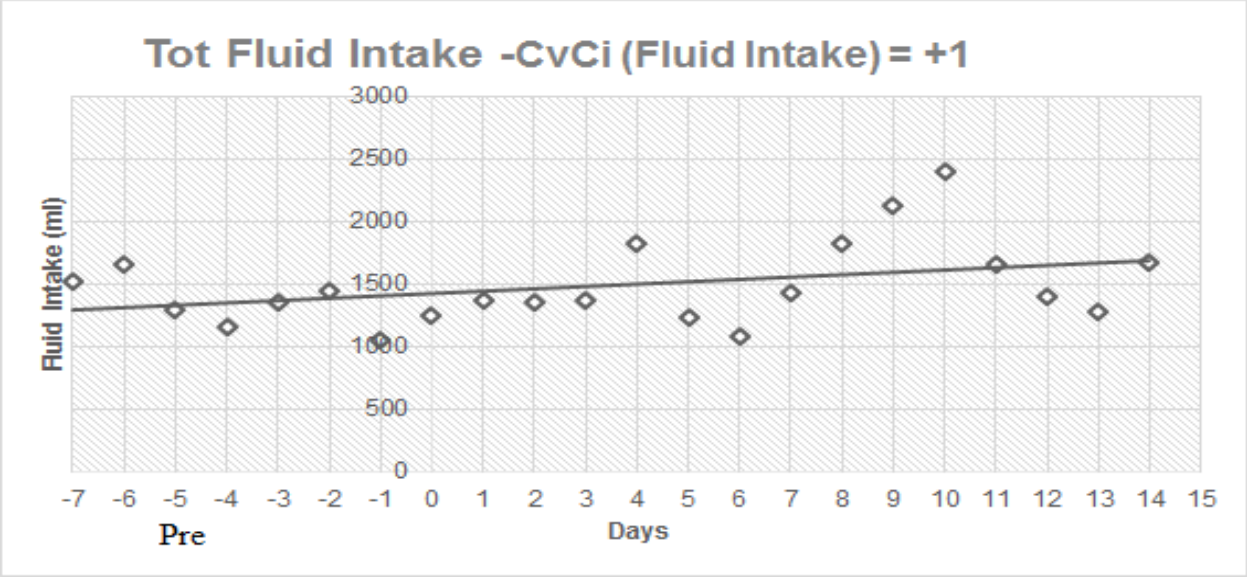

Figure 6b. Trend in total fluid intake Pre-Post Stimulation of a S16 with C*v*C*i* (+1)

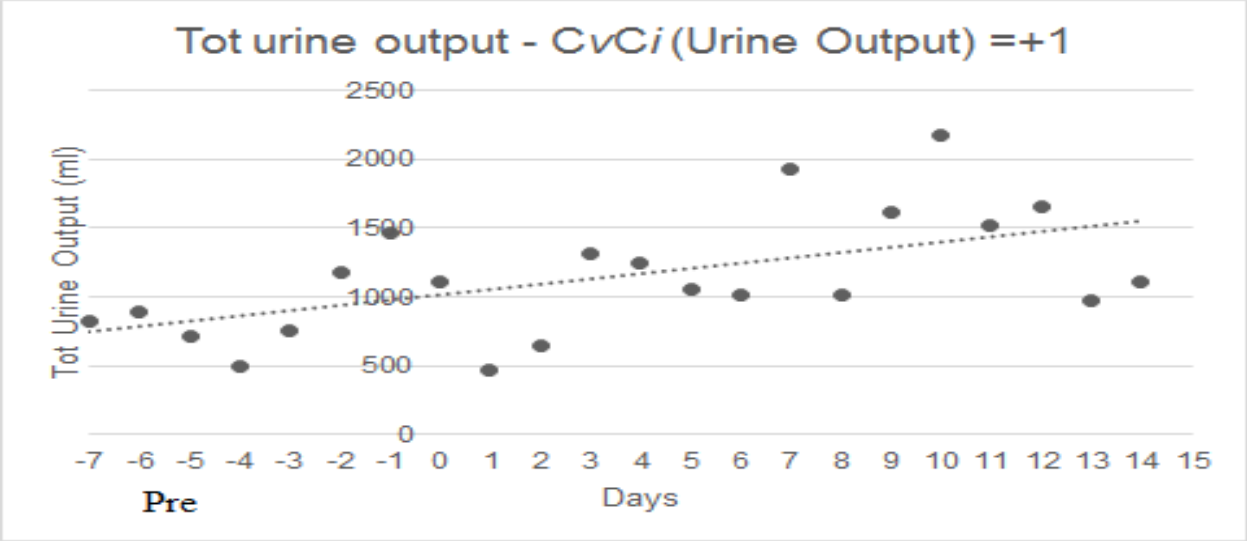

Figure 6c. Trend in total urine output Pre-Post Stimulation of a S16 with C*v*C*i* (+1)

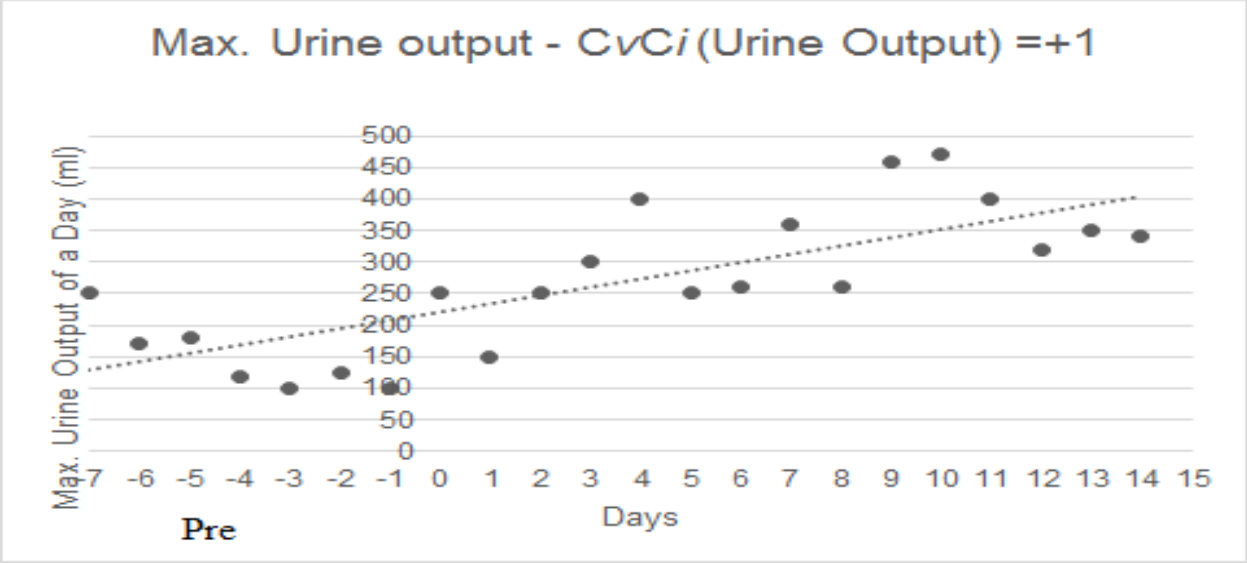

Figure 6d. Trend in max. urine output of a day Pre-Post Stimulation of a S16 with C*v*C*i* (+1)

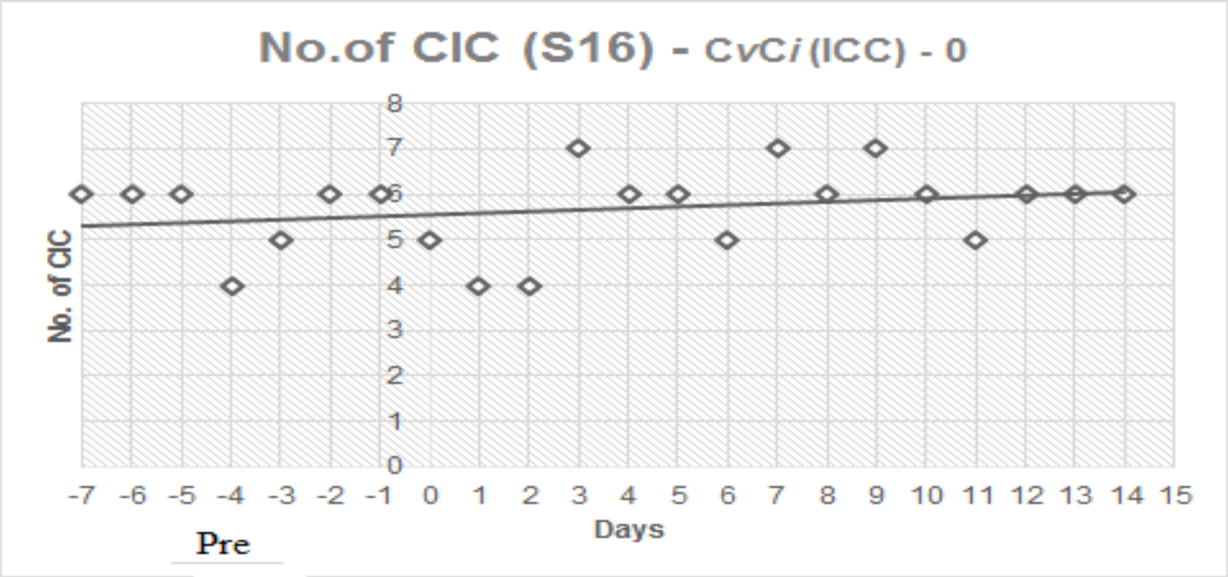

Figure 6e. Trend in Number of CIC Pre-Post Stimulation of a S16 with C*v*C*i* (0)

Cumulative voiding chart index (C*v*C*i*), depicted improvement in 18 subjects while 2 patients did not show any improvement (Table 4). The C*v*C*i* scoring showed that post stimulation 3 subjects had reduced frequency of clean intermittent catheterization, 12 subjects had reduced number of leaks while 7 did not improve in terms of number of leaks and one subject had increased leaks. The C*v*C*i* score further showed increase in total fluid intake per day for 8 subjects and similar number of subjects had improvement in urine output while 12 subjects did not show any change in fluid intake or total urine output per day. 13 subjects had showed improvement in maximum urine output while 7 did not show any trend in improvement. The p-value obtained from Binomial distribution test (p-value 0.001) conducted on improved population against not improved population was found to be significant In regards to satisfaction with feedback questionnaire, all patient were satisfied with treatment methodology and easy to use procedure. Some

patients were happy to observe reduction in number of leaks and improvement in bladder capacity.

Table 4. Cumulative voiding chart index (C*v*C*i*)

Subject.	Frequency of CIC	Δ Leaks	Fluid Intake	Urine Out	Max Output	Total Score
S1	0	-1	0	1	1	1
S2	0	1	0	0	0	1
S3	1	1	0	0	1	3
S4	0	1	1	0	1	3
S5	0	0	0	0	0	0
S6	0	1	0	0	1	2
S7	0	0	0	0	0	0
S8	0	1	0	1	1	3
S9	0	0	0	0	1	1
S10	0	0	1	1	1	3
S11	0	1	1	0	0	2
S12	0	0	1	0	1	2
S13	0	1	0	0	0	1
S14	0	1	0	0	0	1
S15	1	1	1	0	1	4
S16	0	1	1	1	1	4
S17	0	1	0	1	1	3
S18	1	0	0	1	1	3
S19	0	1	1	1	1	4
S20	0	0	1	1	0	2
Scoring Method						
Score for improvement =1 **Score for no change = 0** **Score for deteriotation/worsen = -1**						

Table 5. Binomial distribution test using voiding diary data

Sample size(n)	Improved no. (%)	Not improved no. (%)	Test prop	P-value
20	18 (90%)	2 (10%)	0.5	0.001

Discussion

The patient with spinal cord injury can have secondary complications, which, if not managed properly can cause significant morbidity and mortality. Neurogenic bladder is one of such secondary complication in most of the patients with spinal cord injury. Patients with neurogenic bladder can have frequent urinary tract infection which, if not diagnosed early and treated appropriately, can lead to morbidity and mortality. In the early 1900s, UTI was one of the leading causes of morbidity and mortality in patients with SCI. Over the years, with the improvement in treatment and better understanding the complications due to neurogenic bladder and urinary tract infection has significantly reduced leading to improved active social life. In the patients with SCI due to the loss of supraspinal control, overactivity of detrusor muscles occurs which can lead to small bladder capacity. Patient with detrusor overactivity may have high bladder pressure, vesicoureteral reflux and renal impairment (64). Management of detrusor overactivity by intermittent clean catheterisation along with antimuscarinic drugs is the gold standard for the management of neurogenic bladder in such population. Intravesical agents like Oxybutynin, Propantheline, and Capsaicin, Botulinum-A are also used for the management of urinary incontinence due to overactive neuropathic bladder following SCI. Such medical management have known side-effects with uncertainty in long-term efficacy(20,65).

Sacral neuromodulation, tibial nerve stimulation (66) and pudendal nerve stimulation (67) are the alternative approaches in management of neurogenic bladder, secondary to SCI and are still in research phase. The invasive procedure and varied results limits their usage as a standard of care (68–70). The study conducted at Department of PMR, CMC Vellore(Ojha et el.) (1) was the first to demonstrate neuromodulation technique using surface stimulation of tibial nerve and dorsal penile nerve. The study being non-invasive, easy to implement was very well accepted by the patients undergoing treatment (Ojha PhD thesis)(63).

It has reported that stimulation of the somatic afferent pathways can be an important factor in the efficacy of neuromodulation(71,72). The medial plantar nerve, a branch of posterior tibial nerve in sole of the foot, is a mixed sensory-motor nerve. It contains axons passing through the L4–S3 spinal roots. These sacral roots also contains the peripheral nerves involved in the sensory and motor control of the bladder and pelvic floor and are the same spinal tracts targeted for sacral neuromodulation. Electrical stimulation of these nerves inhibits bladder activity by stimulating large-diameter somatic afferent fibres, which in turn evokes a central inhibition of the micturition reflex pathway in the spinal cord or the brain(73). Results of the pilot study conducted in our department in the year 2009-2011(IRB No CMC/IRB/6735/2008/12/18) showed improvement in leaks as per voiding chart after two weeks of stimulation of posterior tibial nerve(74). In the multicenter, double-blind, randomised, sham-controlled trial, Kenneth et al. found percutaneous tibial nerve stimulation therapy as a safe and effective treatment modality

for overactive bladder symptoms. It also supports the use of peripheral neuromodulation therapy for overactive bladder(75).

Most of the studies mentioned in the literature uses percutaneous stimulation of PTN with a needle electrode (anode) inserted posterior to the medial malleolus and a surface electrode (cathode) over the ipsilateral calcaneus(71–73) and current strength up to 10 mA.

The present study was conducted with the objectives to see if surface electrical stimulation of branch of the tibial nerve, i.e. median plantar nerve at sole of the foot, having same root value, can be used to inhibit detrusor overactivity. Surface stimulation over percutaneous stimulation was preferred to avoid an invasive procedure. In our study, gelled self-adhesive surface pad electrodes were used. The use of pad electrodes was found to be cost-effective and convenient. Surface pad electrodes are easy to use by patients for home-based therapy. The current strength was between 10 - 80 mA and was decided based on the subject's comfort level i.e. maximum current which a person can tolerate or the current strength at which plantar flexion contraction was observed. It is a known fact that to overcome skin impedance the requirement for current strength is higher in the case of surface stimulation as compared to percutaneous stimulation(1). The in-house designed and developed electrical stimulator served the purpose for the required current strength and was found to be cost effective (costing less than 2000 INR).

Our previous study used f-wave test from PTN to check the integrity of spinal reflex arc (Ojha et al)(1). However, f-wave test requires additional expenditure and a visit to

electro-physiology lab. This further delays the treatment plan hence, it was decided to clinically examine ankle jerk as an indicator for integrity of spinal reflex arc.

The quantitative parameters obtained from CMG were reflex-volume, maximum detrusor pressure, cystometric capacity. Though leak point pressure could also have been included in our analysis but there are few patients who did not leak during the time of CMG procedure. Hence this was excluded from the analysis.

Factors such as urinary tract infections and autonomic dysfunction could affect the CMG, especially in patients with neurogenic detrusor overactivity(78).

Due to smaller sample size (in our study -20 subjects), nonparametric Wilcoxon signed rank test was used to analyze CMG data. The p-value obtained from the pre- and post-intervention based on maximum detrusor pressure (p-value - 0.03) and cystometric capacity (p-value - 0.04) was found to be significant and reflex volume (p-value - 0.13) was not significant. In regards to satisfaction with feedback questionnaire, all patient were satisfied with treatment methodology and easy to use procedure. Some patients were happy to observe reduction in number of leaks and improvement in bladder capacity.

The voiding chart is a record of fluid intake and urinary output during a day. Though this method gives true clinical representation of bladder function but there is no index/ score exist which tells the efficacy of state of the bladder using such data. Hence, Cumulative Voiding Chart Index (C*v*C*i*) was conceived as a first attempt towards analysis of

effectiveness of neuromodulation therapy. The C*v*C*i* scoring shows that 18 patients had improvement in bladder capacity / number of leaks /maximum urine output after two weeks of electrical stimulation therapy while 2 patients did not shown any improvement. The p-value showed statistical significant difference between the improved populations as compared to the not improved population suggesting the efficacy of electrical stimulation therapy in improving the state of the bladder,

However, in one patient (S1) though total C*v*C*i* score was +1 due to progressive increase in urine output and maximum urine output in a day, but the subject had increased number of leaks. For this subject increase in number of leaks was observed during the second week of stimulation therapy. On urine culture, it was found that UTI was the main cause of increase in frequency of leaks. The patient was treated for UTI and stimulation was extended for one more week.

In another subject (S20) C*v*C*i* score (+2) showed improvement in fluid intake and urine output though not much noticeable reduction in number of leaks. This can be attributed to non-compliance of the patient to do CIC during night time. Further, examination using transrectal ultrasound revealed condition of open bladder neck. However, this subject had significant improvement in CMG parameters – his cystometric capacity increased by 224%, reflex volume by 80% and there was 27% reduction in maximum detrusor pressure. This case is a true representation of mixed pathology having combination of detrusor overactivity and open bladder neck resulting in urinary incontinence. Though subjects with stress leak falls under the exclusion criteria but for this subject clinical

evaluation at the time of recruitment was more towards complaints of leaks due to detrusor overactivity. The C*v*C*i* scoring was found to be sensitive towards picking up the open bladder neck condition as it represented true progress of bladder function over the time.

For conclusive results, the study has to be conducted on a larger sample size. The noticeable trend in the improvement encourages us to extend the trial to conduct on the large population as well as to validate the C*v*C*i* scoring method.

Conclusions

In this pilot study conducted on 20 patients with spinal cord injury having detrusor overactivity, trend in improvement in bladder function was observed as reported by voiding chart and CMG data with two weeks of daily half an hour stimulation over the sole of foot.

The p-value for reduction in maximum detrusor pressure and increase in cystometric capacity was found to be statistically significant while p-value of reflex volume was not significant in this sample population.

The novel method of quantification of voiding chart data to observe the efficacy of stimulation was conceived as Cumulative Voiding Chart Index (C*v*C*i*). The voiding chart data was categorized into five different categories (Amount of fluid intake per day, Total volume of urine voided per day, Frequency of leaks, Frequency of CIC, Maximum volume of urine output in a day) for C*v*C*i* scoring.

Eighteen patients showed improvement in bladder function while two subjects did not show any signs of improvement as reported by C*v*C*i* score.

However, this method (C*v*C*i*) of analyzing voiding chart data needs to be validated in larger sample-size before it can be used in clinical practice.

There was no adverse effect of the stimulation observed, suggesting that it is a safe treatment and has the potential to become an alternative treatment option for patients with

detrusor overactivity. However, further research on a larger sample is needed to provide statistically conclusive results regarding the efficacy of this treatment and optimal dosage. Further study on the long-term effects of the stimulation and carry-over effect of stimulation will be helpful.

To summarize, neuromodulation by surface electrical stimulation at the sole of the foot is simple, non-pharmacological, non-invasive, inexpensive, promising alternative treatment modality for management of urinary incontinence due to detrusor overactivity.

Limitations of the study

1. The present study is a pilot study with sample size of 20. Its efficiency cannot be compared with standard treatment. For comparison with standard treatment large sample size is needed.
2. The C*v*C*i* scoring was new method and needs validation on large sample size.
3. Long-term effect of the treatment need follow up.

Scope for future research

1. The study can be continued with a larger sample size

2. Follow up of these patients over a longer period of time will help in understanding about the efficiency of treatment over time.

3. C*v*C*i* scoring method can be validated on large population

4. Community trial of stimulator and its benefit can be studied.

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Annexure

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 Re Reg-2016 Issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, D. Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. Antonisamy, Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, MA (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Anna Benjamin Pulimood, MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, MD., DM.,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

November 07, 2019

Dr. Abhinav Singh,
PG. Resident,
Department of PMR,
Christian Medical College,
Vellore - 632 002.

Sub: Fluid Research Grant NEW PROPOSAL:
To study the therapeutic effect of electrical stimulation of tibial nerve at sole of foot in modulating spinal reflex pathways for reducing detrusor overactivity in patients with spinal cord injury: An Interventional study.
Dr. Abhinav Singh (Emp. No. 33897), PG Registrar, PMR, Dr. Jacob George (Emp. No. 30268), PMR, Dr. Rajdeep Ojha (Emp. No. 31799), PMR.

Ref: IRB: 11061 (INTERVEN) dated: 20.12.2017

Dear Dr. Abhinav Singh,

I enclose the following documents: -

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board.

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Dr. Anna Benjamin Pulimood, MD., Ph.D.,
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Ref: IRB: 11061 (INTERVEN) dated: 20.12.2017

Dear Dr. Abhinav Singh,

The Institutional Review Board **(Silver**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "To study the therapeutic effect of electrical stimulation of tibial nerve at sole of foot in modulating spinal reflex pathways for reducing detrusor overactivity in patients with spinal cord injury: An Interventional study." on December 20th 2017.

The Committee reviewed the following documents:

1. IRB Application format
2. Information sheet and Consent form (Tamil, English, Hindi, Bengali)
3. Cvs. Of Drs. Abhinav, Jacob and Rajdeep
4. Profroma
5. Permission Letter
6. Feedback form.
7. No. of documents 1- 6...

The following Institutional Review Board (Silver, Research & Ethics Committee) members were present at the meeting held on December 20th 2017 at 9.45 am in the BRTC, Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Name	Qualification	Designation	Affiliation
Dr. George Thomas	MBBS, D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB, Chennai	External, Clinician
Rev. Dr. T. Arul Dhas	MSc, BD, DPC, PhD(Edin)	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. Shirley David	MSc, PhD	Professor, Head of Fundamentals Nursing Department, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Additional Vice Principal (Research), Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore.	Internal, Clinician
Dr. Prasanna Samuel	MSc, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External,Clinician
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP, FRCPCH	Professor of Paediatrics, Community Medicine, CMC, Vellore	Internal, Clinician
Dr. D. J. Christopher	BSc, MBBS, DTCD DNB, FRCP(Glasg), FCCP(USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Ashish Goel	MBBS, MD, DM	Professor, Hepatology, CMC, Vellore	Internal, Clinician
Dr. Sujith J Chandy	MBBS., MD., PhD., FRCP (E)	Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Dr. Vinitha Ravindran	PhD (Nursing)	Professor & Addl. Deputy Dean, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Abhay Gahukamble	MS, D Ortho, DNB(Ortho)	Associate Professor, Paediatric Orthopaedics, CMC, Vellore	Internal, Clinician
Dr. Jacob John	MBBS, MD, MPH	Professor, Community Medicine, CMC, Vellore	Internal, Clinician
Mrs. Ruma Nayak	M Sc (Nursing)	Professor, Head of Paediatric Nursing & Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "To study the therapeutic effect of electrical stimulation of tibial nerve at sole of foot in modulating spinal reflex pathways for reducing detrusor overactivity in patients with spinal cord injury: An Interventional study." on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:
A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty thousand only) each will be released at the end of the first year as 2 nd Installment.

Yours sincerely,

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board.

IRB: 11061 (INTERVEN) dated: 20.12.2017 4 of 4

PATIENT INFORMATION SHEET

TITLE OF THE STUDY: To study the therapeutic effect of electrical stimulation at sole of foot in improving urinary bladder continence in patients with spinal cord injury: An Interventional study

INTRODUCTION: You are cordially invited to participate in the study to find the therapeutic effect of foot stimulation in improving urinary bladder capacity by reducing number of urinary leaks. We would like to provide certain details about the proposed study which are essential and will help you in making decision for participation.

1.WHAT IS THE PURPOSE OF THIS STUDY?

Due to spinal cord injury urinary leak may occur due to urinary bladder hyperactivity. Current medications and other managements to treat such symptoms has it's own side-effects. Hence, the aim of this study is to study effect of foot stimulation in improving bladder capacity. Duration of this study will be about 4 weeks. One week prior to study all medication related to bladder incontinence will be stopped. You will be asked to maintain voiding chart for 7 days prior to the start of the treatment and during the treatment in which you will be asked to write daily fluid intake, urine output and leaks. Your bladder will be evaluated by standard urodynamics two times i.e. at the start and end of the study period. First bladder examination will be done for screening purpose and if found fit in our inclusion criteria, we will enroll you in the study. Foot stimulation will be given half an hour daily for 2 weeks. You will be asked to fill satisfaction of life

questionnaire at the end of the study. At the end of the study period bladder will be managed as per the standard treatment.

2. WHO WILL PERFORM THE TEST?

The examination, cystometrogram and the electrical stimulation therapy will be performed by the investigators and doctors from PMR department.

3. WHAT ARE THE POSSIBLE COMPLICATIONS?

As such, no life-threatening complication is expected. Electrical stimulation and cystometrogram procedures are routinely done in the department on wide variety of patients.

4. WILL WITHDRAWL OR NON-PARTICIPATION AFFECT THE USUAL TREATMENT?

Withdrawal or non-participation will not affect the usual treatment at present or future. You are free to withdraw from study at any point of time and also free to decide regarding participation.

5. DO I HAVE TO PAY FOR THE INVESTIGATIONS?

You will not have to pay for the foot stimulation treatment and cystometrogram procedure as they are being done as a part of the research.

6. WILL MY IDENTITY AND TEST REPORTS BE KEPT CONFIDENTIAL?

Your identity will be kept confidential and you won't be identified by any means at any time. However, your medical notes may be reviewed by people associated with study, without any additional permission, if you decide to participate in study. Also results of this study will be used for publication in journals and presentation keeping your identity anonymous.

7. IS THERE ANY PROVISION OF COMPENSATION FOR PARTICIPATION?

This study will be done during your stay at the rehabilitation institute and also there is no direct or indirect risk leading to increase in disability or death, hence there is no such provision for compensation. The usage of electrical stimulation and cystometrogram procedure has been found to be safe.

Contact information:

If you have any questions about this research study or possibly, please contact:

Dr. Abhinav Singh,

PG Registrar, Department of PMR,

CMC, Vellore- 632004

Phone number: 09582914688

Email id: dr.s.abhinav@gmail.com

Informed Consent form to participate in research study

Study Title: To study the effect of stimulation of tibial nerve and it's branch in modulating spinal reflex pathways for reducing detrusor overactivity: An interventional study

Study Number: _____

Subject's Initials: _____Subject's Name:

_____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that ***the Sponsor of the clinical trial, others working on the Sponsor's behalf (delete as appropriate)***, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from

the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

(vi) I am aware of the Audio-visual recording of the Informed Consent. [ ]

(Click here for Audio Visual guidelines)

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

Patient feedback questionnaire

Name:

Age:

Hospital number:

Date of admission:

Level of injury:

Cause of injury:

Date of injury:

Start of stimulation:

End of stimulation:

Stimulation Group: A/B/C

Please answer the following questions:

1.What was mode of urination before treatment?

• When was ICC started?

• What was the normal volume of urine discharge per ICC?

2.How many leaks per day did you have before the procedure?

• After drinking how much liquid did you have leaks?

• If you had leaks, then what is the volume of urine collected by ICC immediately after the leak?

3.Did you feel any discomfort during the procedure?

• Very much

• Slightly

• no discomfort

4.How many leaks per day do you have now after the procedure?

• After drinking how much liquid do you have leaks now?

• If you have leaks, then what is the volume of urine collected by ICC immediately after the leak?

5. Overall how do you feel (about urination) after the procedure?

6. Whether the leaks have reduced or increased or still after the procedure?

7. Did you take any medications related to bladder leaks?

• If Yes, then which medications?

• If No then why?

• **Did you stopped any medication related to bladder leaks?**

• If yes then why?

8.Any other comments:

History taken by: