CLINICAL AND ELECTROPHYSIOLOGICAL INDICES AS PREDICTORS OF FERTILITY IN MALES WITH SPINAL CORD INJURY

Experience from a tertiary care hospital in South India

Dissertation submitted to the Tamil Nadu Dr MGR Medical University, Chennai, in partial fulfilment of the requirements for the MD branch XIX (Physical Medicine and Rehabilitation) examination in May 2018

Declaration

This is to certify that the dissertation titled - **"CLINICAL AND ELECTROPHYSIOLOGICAL INDICES AS PREDICTORS OF FERTILITY IN MALES WITH SPINAL CORD INJURY"** is submitted by me in partial fulfilment towards **MD in Physical Medicine and Rehabilitation (Branch XIX)** Examination of the Tamil Nadu Dr M.G.R. University, Chennai to be held in May 2018. It comprises only my original work and due acknowledgement has been made in text to all the material used.

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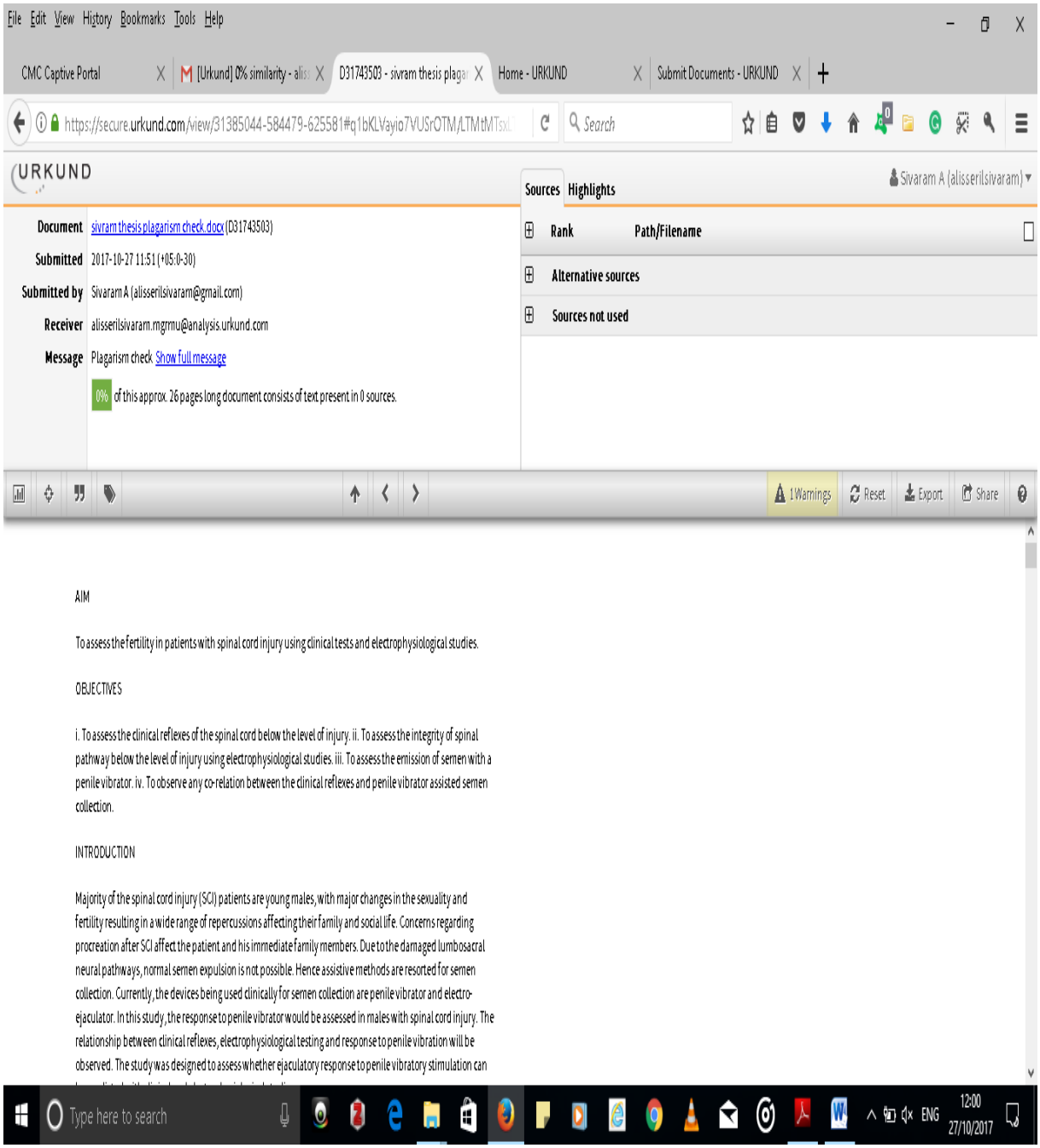

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Table of Contents

LIST OF ABBREVIATIONS USED

SCI Spinal cord injury

PVS Penile vibratory stimulation

fMRI Functional magnetic resonance imaging

IML Intermediolateral cell column

LSt cells Lumbar spinothalamic cells

MEA Medial amygdala

MPOA Medial preoptic area

NO Nitric oxide

nPGi Nucleus paragigantocellularis

PDE5-I Phosphodiesterase-5 inhibitor

PET Positron emission tomography

PVN Paraventricular nucleus of the hypothalamus

BCR Bulbocavernous reflex

HFR Hip flexor response

KFR Knee flexor response

PVN Paraventricular nucleus of the hypothalamus

NANC Non adrenergic non-cholinergic

EEJ Electro ejaculation

IUI Intrauterine insemination

IVF Invitro fertilisation

SEPG Spinal ejaculation pattern generator

SHR Soleus H reflex

PTF Posterior Tibial F wave

LIST OF FIGURES

(XIX) Pie chart plotting the incidence of superficial abdominal reflexes among participants

(XX) Pie chart plotting the incidence of plantar reflex among participants

(XXI) Pie chart plotting the incidence of hip flexor response among participants

(XXII) Pie chart plotting the incidence of knee flexor response among participants

(XXIII) Pie chart plotting the incidence of bulbocavernous reflex among participants

(XXIV) Pie chart plotting the incidence of Soleus H reflex among participants

(XXV) Pie chart plotting the incidence of Posterior tibial F wave among participants

(XXVI) Pie chart plotting the incidence of Somatic responses among participants

(XXVII) Pie chart plotting the incidence of types Somatic responses among participants

(XXVIII) Pie chart plotting the incidence of success rate of trials with PVS among participants

LIST OF TABLES

(XVI1) Table showing sensitivity, specificity, and comparison of ankle jerk vs PVS response

(XVIII) Table showing sensitivity, specificity, and comparison of lower abdominal reflex vs PVS response

(XIX) Table showing sensitivity, specificity, and comparison of plantar reflex vs PVS response

(XX) Table showing sensitivity, specificity, and comparison of hip flexor response vs PVS response.

(XXI) Table showing sensitivity, specificity, and comparison of knee flexor response vs PVS response.

(XXII) Table showing sensitivity, specificity, and comparison of bulbocavernous reflex vs PVS response.

(XXIII) Table showing sensitivity, specificity, and comparison of Soleus H reflex vs PVS response

(XXIV) Table showing sensitivity, specificity, and comparison of Posterior tibial F wave vs PVS response

(XXV) Table showing sensitivity, specificity and comparison of somatic responses vs PVS response

(XXVI) Table showing comparison of types of somatic responses vs PVS response

(XXVII) Table showing comparison of successful PVS response frequency in trials

(XXVIII) Table showing comparison between incidence patterns of BCR & HFR vs PVS response

(XXIX) Table showing Sensitivity and specificity of the combined BCR and HFR pattern

(XXX) Table showing comparison between incidence patterns of BCR & HFR vs neurological level

AIM

To assess the fertility in patients with spinal cord injury using clinical tests and electrophysiological studies.

OBJECTIVES

i. To assess the clinical reflexes of the spinal cord below the level of injury.

ii. To assess the integrity of spinal pathway below the level of injury using electrophysiological studies.

iii. To assess the emission of semen with a penile vibrator.

iv. To observe any co-relation between the clinical reflexes and penile vibrator assisted semen collection.

ABSTRACT

Clinical and electrophysiological indices as predictors of fertility in males with spinal cord injury

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Background: Majority of the spinal cord injury (SCI) patients are young males. Concerns regarding procreation affect the patient and his family members in view of the autonomic dysfunction. The most commonly used assistive method for semen collection is penile vibrator. The study assesses ejaculatory response to penile vibrator stimulation (PVS). Clinical and electrophysiological tests may aid in prediction of this response.

Study Design: Prospective observational pilot study

Objective: To assess the fertility in males with spinal cord injury (SCI) using penile vibrator and to predict the response to PVS using clinical tests and electrophysiological tests.

Inclusion Criteria: Males with SCI, time since injury > 6 months, T6 or below AIS A .

Materials and Methods: Assessment of

(i) clinical reflexes → bulbocavernosus response (BCR), hip flexor response (HFR), cremasteric reflex and superficial abdominal reflexes ,
(ii) somatic responses → abdominal contraction, hip adduction during stimulation
(iii) electrophysiological responses → H reflex from Soleus and F wave from tibial nerve
(iv) Response to PVS (1,2)

Results:

Among the 23 patients recruited, seven had successful ejaculation with PVS (responders). All persons with T6-T8 neurological level of injury (n=4) and three among persons with neurological level T9 - T12 (n=19) were responders. Among these seven patients, 6 patients

had somatic responses during stimulation, whereas, two of the responders showed correlation with electrophysiological tests.

Clinical reflexes	Frequency	Responder frequency	Sensitivity	Specificity	P value
Neurological Level T6–T8	4	4			**0.004**
Neurological Level T9–T12	19	3			**0.004**
Bulbocavernous Reflex	15	5	72	37.5	1.000
Cremasteric Reflex	0				
Superficial Abdominal Reflex(T10–T12)	8	3	42	68.75	0.660
Plantar reflex	9	3	42	62.4	1.001
Hip flexor response	7	2	28	68.75	1.000

Somatic responses	Frequency	Responder frequency	Sensitivity	Specificity	P value
Abdominal contraction	5	4	56	93.75%	0.75
Hip Flexion	5	3	42	87.5	0.75
Hip adduction	1	0			
Paresthesia in the sole of foot	2	1	14	93.75%	0.785
Electrophysiological Studies	**Frequency**	**Responder frequency**	**Sensitivity**	**Specificity**	**P value**
Soleus H reflex	7	2	28	54	0.185
Posterior tibial F wave	7	2	28	54	0.185

Conclusion: Level of injury is a predictor of fertility using PVS in males with spinal cord injury.

References :

1. Bird VG, Brackett NL, Lynne CM, Aballa TC, Ferrell SM. Reflexes and somatic responses as predictors of ejaculation by penile vibratory stimulation in men with spinal cord injury. Spinal Cord. 2001;39(10):514–519.

2. Brackett NL, Ibrahim E, Iremashvili V, Aballa TC, Lynne CM. Treatment for ejaculatory dysfunction in men with spinal cord injury: an 18-year single center experience. J Urol. 2010;183(6):2304–2308.

INTRODUCTION

Majority of the spinal cord injury (SCI) patients are young males, with major changes in the sexuality and fertility resulting in a wide range of repercussions affecting their family and social life. Concerns regarding procreation after SCI affect the patient and his immediate family members. Due to the damaged lumbosacral neural pathways, normal semen expulsion is not possible. Hence assistive methods are resorted for semen collection. Currently, the devices being used clinically for semen collection are penile vibrator and electro-ejaculator. In this study, the response to penile vibrator would be assessed in males with spinal cord injury. The relationship between clinical reflexes, electrophysiological testing and response to penile vibration will be observed. The study was designed to assess whether ejaculatory response to penile vibratory stimulation can be predicted with clinical and electrophysiological studies.

REVIEW OF LITERATURE

Spinal cord injury is defined as any injury to a segment or segments in spinal cord resulting in sensory and motor damages, leading to functional changes in locomotion, sensory perception, sexual function and bladder and bowel function.(1) This could be a result of trauma which can occur in multiple ways like fall from height, road traffic accidents, fall of heavy objects on back, high velocity sport activities, diving accidents, gun shots and assault with other weapons.(2)

It is still intriguing that spinal cord injury even though being mentioned 4000years back in Edwin Smith Papyrus, the treatment still remains an enigma as there is no proven curative medication or procedure till date. By the end of first and second world war, in view of the larger number of the spinal cord injured soldiers, spinal cord injury units were started in a few renowned centres in America and other developed countries. Meanwhile the conservative and surgical options of management of spinal cord injury improved with various forms of skeletal traction including Halo Vest to better stabilisation surgeries using Harrington‘s distraction and compression rods.(2) Pioneers like Dr Donald Munro, Dr Sir Ludwig Guttman, Sir George Bedbrook, Ernest H. J. Bors, Estin Comarr and John Young showed the world through their work that treating the injury to spine is not enough in managing the condition. They stressed the need for comprehensive care including the prevention of secondary complications like infection, pressure ulcers and contractures, improving the functionality of the patient by exercises, providing psychological and social support by various options

like vocational training and community reintegration. Dr Air Marshal Amarjit Singh Chahal pioneered for setting up a spinal cord injury unit in India for the soldiers of war who met with a spinal cord injury. Dr Mary Varghese popularly known as the wheelchair surgeon who herself being a paraplegic set up a spinal cord injury centre in Christian Medical college Vellore. (2),(3)

Although curative options for spinal cord injury are non-existent currently, the lifespan of patients post spinal injury has improved significantly and are better integrated into the society following the advent and growth of rehabilitation services, environmental modifications and laws which ensures rights or reservations to persons who are differently abled. (2)

The epidemiological reports of spinal cord injured persons in developing countries are scarce. It is probably due to the absence of the national spinal cord injury programmes and registries and lack of proper hospital records in vast majority of these developing countries. According to the reports, the rate of developing spinal cord injury in persons ranges from 2.3 to 83 per million every year and there is an alarming trend of rise in incidence with an increase in motor vehicle accidents the major factor. The number of spinal cord injured persons in the general population ranges from 236 to 1009 million.(4) According to studies, the rate of developing new spinal injury was around 15 per million per year in India which translates to about 20000 new cases per year all over India. Majority are from lower socioeconomic strata and nearly half of them result from fall from trees or roof or electric post. About one third of the spinal

cord injury occurs following road traffic accidents. As per WHO estimates, the incidence of this condition is on the rise in developing countries like India as the load of motor vehicles on the road has climbed steadily without much change in the transport system and infrastructure. (4)

Author	Year	Incidence (Per million)	Prevalence (per million)	Age	Gender ratio	Most common mode of injury
Tidsski	2012	20	236	20 - 50		Fall from height
Lalwani	2014	---	---	25 - 64	84 : 16	Road traffic accident
Chacko	1986	--	125	30 - 40	92 : 8	Fall from height
Singh	2003	20	483	35.4	Men	Fall from height
Agarwal	2007		107		83 : 17	Fall from height
Pandey	2007		60	34	85 : 15	Fall from height

Table (i) Table showing epidemiological studies of spinal cord injury in India

In a recent study held in India, more than a third of patients were in their thirties with males being more commonly affected with the male-to-female ratio ranging from 4.5:1 to 13.5: 1 in multiple studies. Falls are the most common cause followed by road traffic accident in developing country like India. (4)

Adopting bladder management plans like self-intermittent clean catheterisation / suprapubic catheterisation have resulted in reduction of renal complications and thereby increasing the lifespan. Other causes of death in spinal cord injury patients are pneumonia, pulmonary embolism or other thrombotic disorders and septicaemia.(2) Among the individuals with a spinal cord injury, 10% of high level tetraplegics and about 5% of paraplegics die of various causes in the first year. In those who survive the first year, 47% tetraplegics and 62% paraplegics live beyond 40 years of injury. (5) The management of spasticity and neurogenic pain has improved the quality of life of spinal cord injured.(2) In addition, there are various options available to improve mobility following spinal cord injury.

One other factor to further improve the quality of life is addressing the sexual issues following injury. Studies have shown that addressing sexual and fertility issues can have profound effects on adding value to life in these persons.(2) In a study, about 25% of participants with paraplegia ranked regaining sexual function as the most important factor for improving the quality of life while about 13% tetraplegics had a similar opinion. There was not much difference in the ranking by acute and chronic spinal injured patients. When spinal injured persons were asked about the main priority for continuing sexual activity even after injury, more than 50% addressed the same as to maintain intimacy, other responses were to satisfy sexual need, to improve self-esteem, for partner satisfaction and for fertility.(6)

William Masters and Virginia Thompson proposed a four stage physiological model of human sexual response namely arousal (excitement), pre orgasmic (plateau),

orgasmic, and resolution. The arousal phase comes initially following the stimulation which can be either genital or psychogenic. The plateau phase starts with rising pulses, palpitation and tachypnoea and increased tone in the muscles. External urethral sphincter contraction for preventing the retrograde ejaculation occurs at this stage along with the contraction of bulbocavernosus rhythmically. In the orgasmic phase there is a sudden burst of pelvic floor muscle contraction. Later, in the resolution phase, both skeletal and smooth muscle relaxation occurs.

Sexual instincts issues has a wide theme and scope, and extends beyond physical attraction and the urge to procreate. It is a core part of being an individual which involves owns perception of gender, assuming roles in family, expressing the sexual desires, enjoying the sexual pleasures, feeling intimate with family and it aids in procreation. Since it is influenced by social, psychological, economic, cultural and religious factors, rehabilitation for the same should be a comprehensive one. Sexual rehabilitation brings about improvement in the body image and providing the emotional support for the person with spinal injury.(7)

Spinal cord injury (SCI) adversely affects both sexual instincts and procreation. The severity will depend on the level of injury, completeness of lesion, drug interactions, coexisting comorbidities and time duration since injury. The ability of persons with spinal cord injury to have progeny not only depend on the above factors, but also on the characteristics of semen, partner fertility, semen collection methods and artificial insemination techniques.

Low fertility among males with spinal cord injury is often due to damage to the spinal pathways responsible for successful ejaculation, hypercontractile bladder with high reflex pressures / recurrent urinary tract infections, frequent orchitis and poor temperature control in the testes. The failure of these mechanisms lead to reduced / near normal sperm counts, reduced sperm motility, dysfunction of prostate and other accessory glands, increased cytokine concentration, autoantibodies / inhibitory factors against sperms in seminal fluid and increased oxidative free radicals which further increases the damage. When compared to an adult male of the same age, the amount of motile sperms in males with spinal cord injury is less than one third of that found in adult males of same age.(8)

Sexual functions to be addressed in persons with spinal cord injury are erection, emission, ejaculation and orgasm. In persons with spinal cord injury these are present to a certain extent, however, they are altered significantly. (9)

Erection is mediated the activity of the parasympathetic system which will cause the relaxation of the smooth musculature and spiral arteries of corpora cavernosa which will thereby cause the compression of the sub-tunical veins and thereafter arterial flow maintains erection. Erection is of two types, reflexogenic and psychogenic. Reflexogenic erections are produced by the genital stimuli which activates the parasympathetic centre in S2 to S4 spinal segments via the pudendal nerve and subsequently causes erection through the pelvic nerves and Non Adrenergic Non Cholinergic (NANC) fibres. Psychogenic erection is orchestrated by the stimuli through the hypogastric nerve from the supraspinal centres and the sympathetic centre

located in the intermediolateral grey column. Currently erectile dysfunction can be managed by use of different agents / techniques including oral pharmacological agents like Phosphodiesterase 5 inhibitors (Sildenafil, Tadalafil), perurethral agents like Alprostadil (Medicated Urethral System for Erection), injectables like Papaverine / Alprostadil and non-pharmacological methods like Vaccum devices and penile implants.(10,11)

One in ten of the spinal cord injured males have the ability to ejaculate per urethra during intercourse or stimulation. The rest will need some medical intervention to collect semen and thereby aid procreation. (11)

Ejaculation is coordinated by somatic and autonomic nervous system, and consists of two main phases: emission and expulsion. The structures involved in this process are epididymis, vas deferens, seminal vesicles , ejaculatory ducts, bladder neck, external urethral sphincter , the cowpers gland , urethral and periurethral musculature.(11)

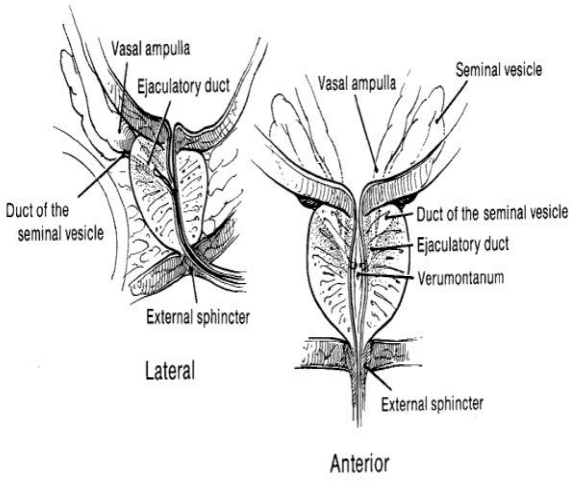

Figure (I) showing the anatomy of ejaculatory pathway (11)

Multiple theories have been proposed to explain the mechanism of ejaculation. One such theory explains the process by a two part model consisting of emission and expulsion with formation of a pressure chamber in posterior prostatic urethra by the simultaneous closure of the distal and proximal sphincters and filling up of that resulting space with the secretions from the ejaculatory duct. Intermittent contraction / relaxation of the three layered muscular wall of vas deferens and ejaculatory duct along with closure of the distal and proximal urethral sphincters are produced by norepinephrine mediated sympathetic fibres which originates from the intermediolateral column cells of T10-L2. At a particular pressure threshold the bulbocavernosus muscle will start contracting along with intermittent relaxation and contraction of the external sphincter. This results in expulsion of semen at a pressure of about 5 meters of water. (10, 11)

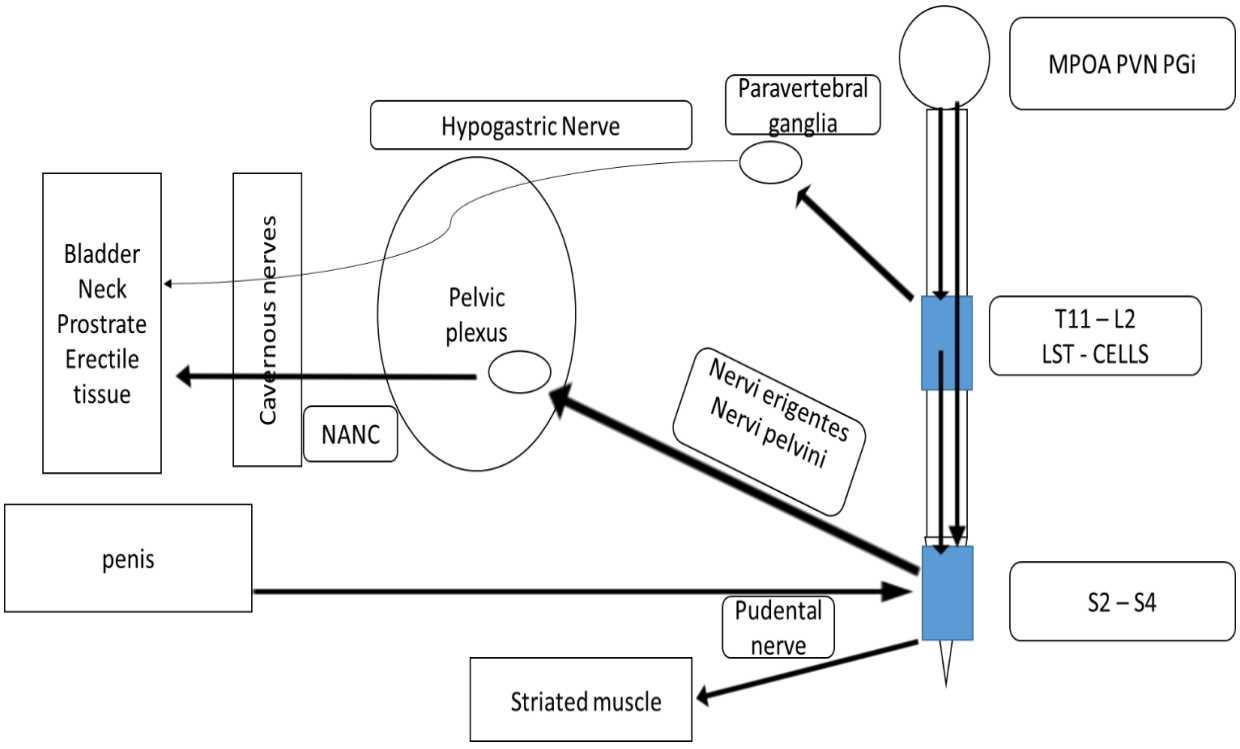

Figure (II) showing the neuroanatomy of emission and expulsion

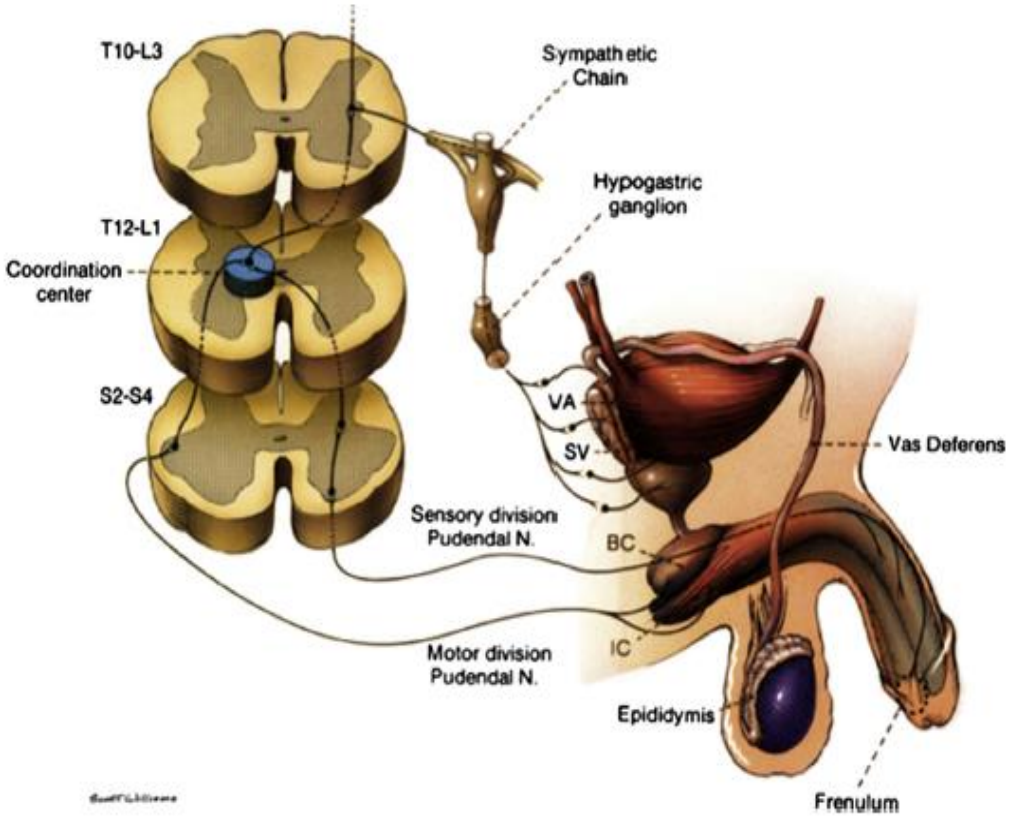

Figure (II) showing the neuroanatomy of emission and expulsion (12)

The sensory input from the genitalia passes through the dorsal penile nerve, the pudendal nerve and then to the S2-4 segments of the spinal cord. Nerve fibers from this region pass to the intermediolateral column cells located in the T12-L2 area of the spinal cord, which help in orchestrating the process of emission. Axons from these cell bodies travel along the ventral roots synapsing in the peripheral sympathetic ganglia and the postganglionic fibers of the same orchestrate the process of emission. Initial process in emission is the closure of urethral neck and internal urethral sphincter for the semen to go anteriorly into urethra than to the bladder posteriorly. Somatic motor nerve fibers originate from the Onuf's nucleus in the ventral horn of S2-4 spinal segments and pass through the perineal branch of the pudendal nerve to

supply the external urethral sphincter and peri-urethral muscles which aid in directing the contents of the posterior urethra in an ante-grade direction. The above mechanism was scrutinized with the help of per rectal ultrasound which showed no evidence of any pressure chamber. Researchers studied the electromyographic recordings of bulbocavernous muscle and the effect of incremental infusion of saline in the posterior urethra, observation was that the muscle contraction occurred at increased volumes. Thus pressure chamber hypothesis was not able to explain the rare ejaculatory sequences which do not result in expulsion of semen (Dry ejaculation).(13,14)

In an experimental animal model, researchers found a centre which is capable of coordinating rhythmic contractions in the perineal muscles resulting in emission and named it as Spinal Ejaculation Pattern Generator. The lumbar spinothalamic neurons helps in relaying sensation from the genitalia to the centres in the brain like nucleus paragigantocellularis (nPGi), hypothalamic paraventricular nucleus (PVN), medial preoptic area (MPOA) and also coordinate with the sacral parasympathetic centres in this process. When researchers, blocked the activity of these centre with a neurotoxin, the whole process of emission failed to occur. Thus, showing that lumbar spinothalamic neurons acts as spinal ejaculation pattern generator by coordinating both the sympathetic and parasympathetic system involvements in process in ejaculation as well as sending impulses to the parvocellular subparafascicular nuclei in thalami and thereby aiding the process of orgasm.(11,15,16)

In another study using PET scanning, the effects of ejaculation and orgasm in human and rat brain was assessed with the change in blood flow to various areas of brain. It

was observed that the junction between the mesencephalic and diencephalic areas of brain is activated more during ejaculation in humans. Meanwhile amygdala and medial preoptic area were highly active areas in rats, hence the study proved that ejaculation pathway has some major differences in humans and rats.(11,15,17)

Serotonin has an inhibitory effect on ejaculation by activating the medial frontal lobe pathways. The area concerned is the medial preoptic area which inhibits the dopaminergic stimulatory area in hypothalamus called the paraventricular nuclei and thereby prevent ejaculation.(9,18)

Adrenergic agents act via the activation of stimulatory centre in brain called the paragigantocellular nuclei located in the brainstem. So patients with acquired brain injury will have problems in all phases of ejaculation.(9,19)

Parkinsonian patients who were started on Levodopa showed sexual adverse effects like ejaculatory disturbances. This suggests that Dopamine is also involved in the ejaculatory circuit. There are 5 types of dopamine receptor. D1 receptor inhibits the ejaculatory response while D2 & D3 receptors facilitates it. The effect is dose dependent.(20,21)

In small animals like rats, intact connections to the supraspinal centres are essential for ejaculation to occur, unlike, in humans where ejaculation can still occur even if the relay to higher centres are disrupted. It was proposed that in humans, a spinal reflex ejaculation pattern generator is present which is situated in lumbar area extending

from L2 which contain lumbar spinothalamic cells which provide the stimuli for timely sequencing of ejaculatory process. They have high levels of C Fos protooncogenic peptide activity at the time of ejaculation and are the direct relay centres of thalamic paragigantocellular nuclei. C Fos is thereby an ejaculation specific peptide. The chemical which help in transmitting the stimuli along the neuromuscular and neuronal junctions is Glutamate and the receptor responsible for the same is NMDA receptor. Other chemicals which were observed in the transmission are α amino 3 hydroxy 5 methyl isoxazole propionic acid and Neurokinin. The influx of stimuli comes from higher centres in brain by anterolateral column. Meanwhile local sensations pass along pudendal nerve branches like dorsal penile nerve and anterior urethral nerve and reach the sacral parasympathetic centre and from there it reaches to the lumbar spinothalamic cells. Any loss of perceiving these sensations will lead to prolonged duration for ejaculation but it doesn't cause any loss of ejaculatory response.(9,10,22–25)

In human body, there is a 30 aminoacid long neuropeptide which got its name from the amino terminal Glycine and carboxy terminal Alanine called Galanine which was discovered in 1978 in Sweden. It was seen in high concentrations in brain, gut, adrenal gland and spinal cord. It mainly influences functions like memory, addictions, seizure activity. In brain the most galanin concentrated area is Hypothalamus and it is one of the supra-spinal centres of control for ejaculation. In the rat spinal ejaculation pattern generators, the amount of galaninergic neurons were high. This area in male rats are not seen in females which shows that it is a sexual dimorphic area. So inorder to evaluate the presence of the centre in humans , initially cadaveric study of the

segments from L2 - L5 was done and later a retrospective study for finding out the efficacy of penile vibratory stimulation in spinal cord injured males was done. It was found that galaninergic neurons are present located between L2 and L5 segments in medial lamina VII on both sides of the central canal, with maximal concentrations within the L4 level. Concentration of the neurons are higher in men than women which states that it is a sexually dimorphic structure. In the patient population they studied, injury to the L3–L5 segments was the only predictor for successful response after PVS trials. The successful response rates were high, when the L3-L5 segments were spared. (26,27)

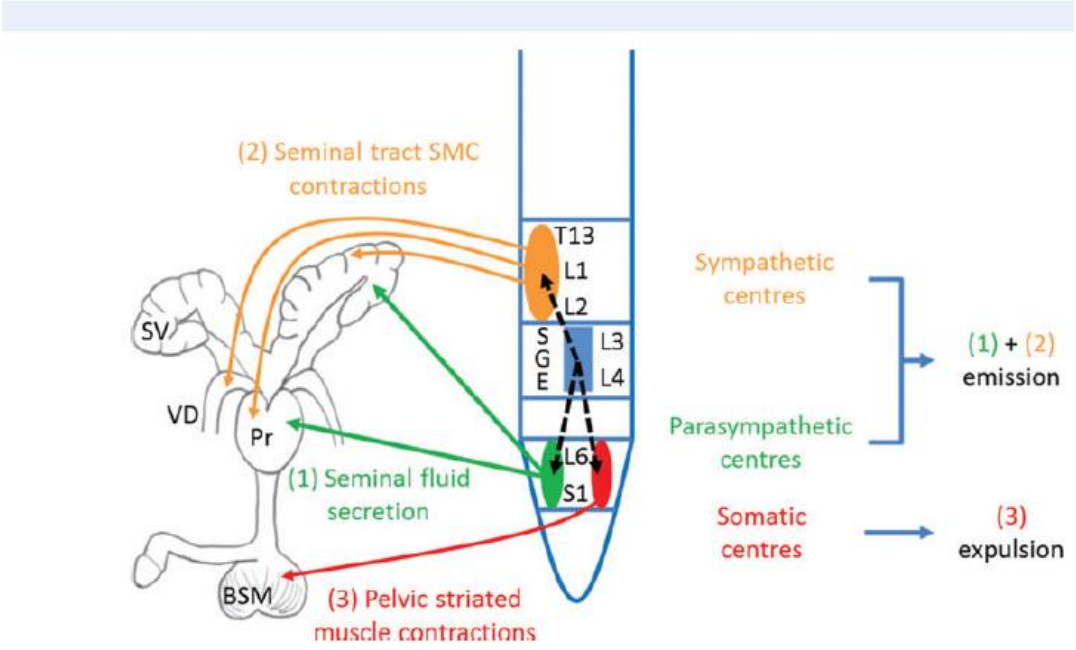

Figure (III) showing the neuroanatomy of human spinal ejaculation generator (26,27)

The response to the genital / supraspinal stimuli originates from the lumbar group (L3-L5) of nuclei called spinal ejaculation pattern generator (SEPG). The relay impulses from the SEPG stimulate the nuclei in the spinal intermediolateral grey horn of T10 – L2 spinal segments (Sympathetic neuronal centre). From here, the association fibres

pass to paravertebral ganglion where most fibres do not synapse with the nuclei inside the ganglion. These fibres are short and later project to superior hypogastric ganglion which is near the bifurcation of aorta. All the fibres from the ganglion join the hypogastric nerve and supplies the bladder neck, prostate, vas deferens and corpora cavernosa through the pelvic nerves and cavernous nerves. These fibres are having a long course and they help in mediating the ejaculatory response along with the somatic and parasympathetic fibres. There are two other circuits through which sympathetic impulses can reach its target site even if the hypogastric nerve is not intact. They are (i) from the paravertebral ganglion to the pelvic nerve and (ii) from paravertebral ganglion to the pudendal nerve. The cavernosal nerves are more involved in erection and act via NANC fibres where nitric oxide(NO) is the neurotransmitter. (17,24,25,28,29)

When the lumbar spinothalamic cells of mice were ablated, it lead to anejaculation even though erection and sexual drive were intact. In rats and other smaller animals, intact connection with higher centres are essential for ejaculation, while in humans it's not required, which was first postulated in 1948.(30)

Ejaculation can be triggered by electrical stimulation of dorsal penile nerve which was more successful in patients with complete lesion of spinal cord and neurological level above T10. This is possible through triggering of ejaculatory reflex by stimulating the spinal ejaculation pattern generator. In patients with complete spinal cord injury, about 4 out of 5 patients were able to expel semen by penile vibratory method while only one out of ten patients were able to have successful ejaculation through natural

methods. Blocking the dorsal penile nerve will result in inhibition of ejaculation while anesthetising the urethra was found to have no effect.(31,32)

When guanethidine a centrally acting antiadrenergic drug was administered, there was inhibition of emission but there was no change in ejaculation post sexual activity and electrostimulation. α-receptor antagonists like phenoxybenzamine or cystoprostratectomy were not able to inhibit ejaculation. Radical prostratectomy causes loss of autonomic ejaculation while somatic ejaculation is preserved. This proves that emission is not the trigger but it facilitates ejaculation. Emission starts with closure of the bladder neck and internal urethral sphincter by sympathetic control followed by secretion of seminal contents by parasympathetic pathways. But the last part of emission is rhythmic contraction of vas deferens which is mediated by sympathetic pathways.(29,33,34)

Persons with spinal cord injury lesions above T10 level with an intact paravertebral sympathetic ganglion and its postganglionic fibres, will be able to have erections reflexively following genital stimulations while they will not be able to have a psychogenic erection. They might not be able to have nocturnal ejaculation. These individuals are likely to be successful responders to both penile vibrator and electroejaculator stimulation.(10)

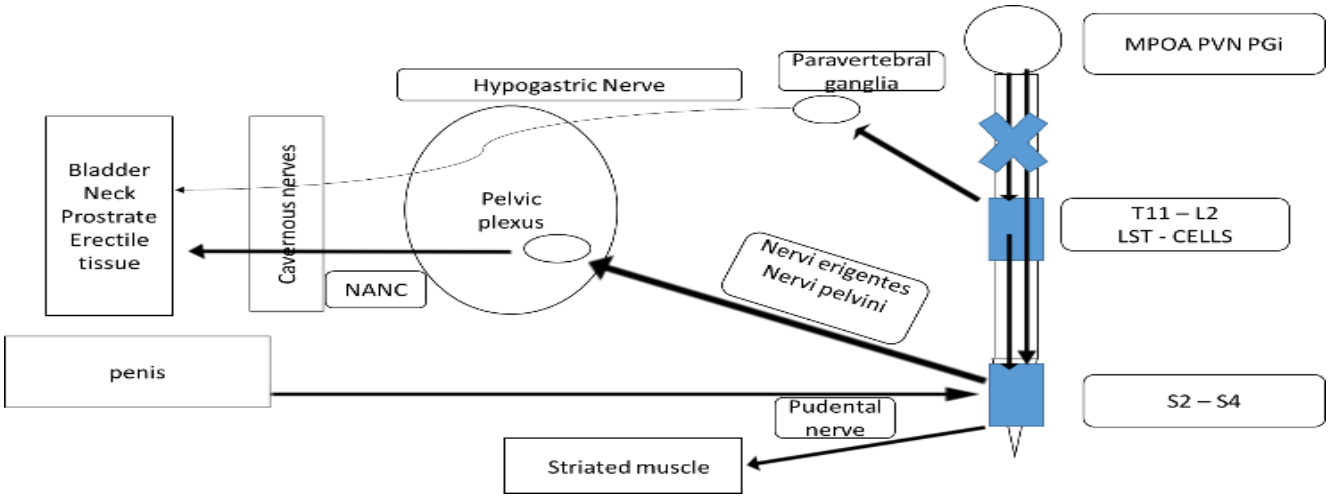

Figure (IV) showing the neuroanatomy of emission and expulsion in above T10 lesions.(10)

In patients with lesions between T10-L2 neurological level will have reflexive erections, but not have psychogenic erection. But some of these patients can have psychogenic erections, because of neuroplasticity in the spinal cord following the lesions and intactness of the preservation of the parasympathetic paravertebral ganglia. Only ejaculation by electroejaculator is possible as the postganglionic fibres are needed for the same.(10)

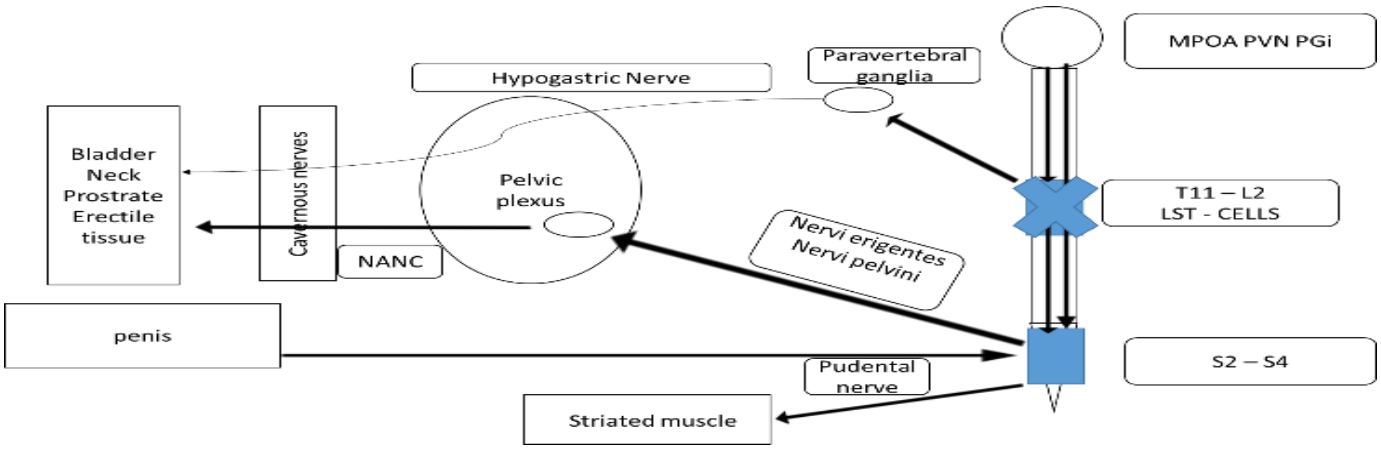

Figure (V) showing the neuroanatomy of emission and expulsion in T10 – L2 lesions.(10)

In those who have lesion between the thoracolumbar and sacral centres, sometimes psychogenic erections are present along with reflexive erections due to the presence of a weak sympathetic tone. Electroejaculation can occur in these patients.(10)

Patients with lesions in S2-S4 neurological level or below can have psychogenic erection while reflexive erections are absent. It can be attributed to the adrenergic receptor mediated erection, interconnection between NANC, adrenergic receptor, and parasympathetic nuclei or preserved NANC. Nocturnal ejaculation can be present. Electroejaculation can occur only if parasympathetic postganglionic fibres are intact.(10)

Because of the complexity of the events involved in ejaculation, its very difficult to predict ejaculation. Hence there is a paucity of literature in this area. Spinal cord injured persons with neurological level above T10 are likely to have success with

penile vibratory stimulation while those with level below T10 are likely to have a significantly lesser success rate. In about 4 in 5 of spinal cord injured persons above T10, were able to ejaculate with a frequency atleast 80 Hz and amplitude more than 3.5mm. When tried with a penile vibrator of lesser frequency, the efficacy in attaining successful response drops to about 60%. Ejaculation was enhanced with use of alpha receptor stimulant drugs like eserine, midodrine, and physostigmine. Electro ejaculation of the pelvic, hypogastric and sacral nerves cause ejaculation in 95% patients with spinal cord injury. Even in complete ablation of spinal cord, if prevertebral ganglia and hypogastric nerve are preserved, electrostimulation can be successful.(10,37)

Since the organs in pelvic cavity have two discrete sets of neural supply and due to development of a process call neuronal plasticity, in some persons with spinal cord injury after a period of time the ejaculatory reflex may appear or get better. Hence the penile vibrator and electroejaculator may be useful methods of semen collection in these patients in future. For a successful penile vibratory response, an intact reflex pathway is needed and for successful electroejaculatory response, functionally preserved post-ganglionic fibres are needed. (38)

In a study done with the use of neurotropic viruses, the genital stimuli went along the dorsal penile nerve to the circuits relaying to the supraspinal areas and to nuclei dorsal to the sacral preganglionic area. The study also revealed that there was no relay of impulses to hypogastric and pelvic neural network. Penile ring block focusing on dorsal penile nerve inhibits ejaculation. Ejaculation using penile vibrator is achieved

after stimulating the dorsal penile nerve and it is the most effective method for semen retrieval in persons with anejaculation. Intactness of the sacral reflex arc and thereby intact pudendal nerve which is elicited by the bulbocavernous reflex, helps in predicting the ejaculation. Nocturnal ejaculation which is also known as autonomic ejaculation is not well described by these studies.(10,39)

When thoracolumbar prevertebral ganglional neurons were given electrical stimulation, there was resultant contraction of the vas deferens and nearby structures leading on to emission and ejaculation. Musculature of Vas deferens contracts in a rhythmic fashion from proximal to distal with the stimulation of the neurons. It concomitantly produces contraction of the bladder neck, prostrate and seminal vesicles. It can be enhanced by the use of alpha receptor mimetic drugs and instillation of muscarine. Hypogastric nerve when cut or damaged will inhibit the ejaculatory process. Electrical stimulation of the pelvic and dorsal penile nerve also result in ejaculation. But expulsion of sperm following electrical stimulation of dorsal penile nerves can only be partly blocked with the help of atropine. But damage to the pelvic nerves will not interfere with the ejaculation post electrical stimulation of dorsal penile nerves showing that they may be working by two different pathways.(10)

Adrenergic agents have a major role in contraction of the vas deferens musculature, bladder neck and prostate while cholinergic agents are responsible for contraction of seminal vesicles and secretory function of male accessory glands like prostate, seminal vesicles and distal epididymis. Thus adrenergic agents have a greater role in ejaculation. This view is strengthened by the clinical effectiveness of ephedrine which

is an adrenergic agent used for retrograde ejaculation. Erection occurs during cholinergic activity, during which there will be secretion of seminal fluid contents by accessory male glands and this fluid is pushed into vas deferens by distal epididymis contraction. It thereby relates with the emission part of ejaculation. It is then succeeded by the adrenergic phase, which causes rhythmic sequential contraction of vas deferens, bladder neck and prostrate help in increasing the pressure inside posterior urethra and later, impulses through the pudendal nerve cause rhythmic contractions of bulbocavernosus muscle.(9,19,40)

The innate ability of vas deferens musculature to have rhythmic contractions while being stimulated by the secretions in the posterior urethra is central for ejaculation. Factors like denervation of the dorsal penile nerve, blockade of adrenergic and cholinergic transmission has no effect on rhythmic muscle activity in the vas deferens while neuromuscular blockers when given to vas deferens stopped ejaculation.(32,41)

In a retrospective study done in University of Miami Miller school, the predictable factors of ejaculation other than the level of spinal cord injury and the amplitude of vibrations delivered through a penile vibrator were explored. It was proposed that even though level is best predictor for ejaculation, factors like Bulbocavernous reflex, hip flexor response and reflexes that occur in persons with spinal cord injury while they undergo penile vibratory stimulation can also help not only in prediction of success rate as well as the adequacy of stimulation but also to decide when to call off the trial of penile vibratory stimulation. They proposed that regardless of the presence or absence of the above mentioned reflexes, penile vibrator stimulation is the method

of choice for semen collection in patient with cervical spinal cord injury. While the presence of bulbocavernous reflex and / or pathological hip flexor response will significantly increase the chances of ejaculation than in those with absent reflexes. This is significant in males with upper thoracic (T1-T6) and lower thoracic (T7-T12) level of lesions in whom the rates of ejaculatory was 70% and 35% respectively more than those who had absent reflexes.(36,42)

The reflexes that appeared during penile vibrator stimulation were abdominal contraction, lower limb withdrawal responses, flexor spasm, hip abduction, hip adduction and piloerection.(43) Abdominal reflex contraction were noted in nearly 90% of the spinal cord injured persons irrespective of the level of injury and ejaculatory response, Abdominal contractions have a low prediction rate. Piloerection was showing significant prediction rate with lower thoracic level patients while withdrawal response, thigh abduction and adduction response were showing a similar prediction in upper thoracic spinal cord injured patients. When these responses were present, they were associated with ejaculation in 4 out of 5 patients.(36)

The integrity of these reflex arcs can be assessed by clinical tests (i) Bulbo-cavernous reflex, (ii) Cremasteric reflex, (iii) Lower abdominal reflex, (iv) Ankle jerk (v) hip flexor response and (vi) electrophysiological tests. Electrophysiological tests (VIa) Soleus H reflex and (VIb) Tibial F wave.

(i) Bulbocavernosus reflex tests the integrity of S2 -S4 segments. . In earlier studies, absence of bulbocavernous reflex was seen as a poor prognostic indicator of ejaculation with PVS.(43)

(ii) Cremasteric reflex tests the integrity of L2 segment,

(iii) Lower abdominal reflexes tests the integrity of T10 to T12 segments and

(iv) Ankle jerk tests the integrity of S1 segment (44)

(v) Hip flexor response is a flexion response which is not seen in normal patient but in patients with SCI and a neurological level above L1. A firm stroke on the lateral aspect of the sole of the foot (S1) produces hip flexion (L2 ± L4) which indirectly indicates that the segment from S1 to L2 are intact. In about 75% patients with the reflex had successful response to penile vibratory stimulation.(43,45,46)

(VIa) The H reflex (Hoffman reflex) from the soleus tests the S1 spinal segment. It is the simplest record of ankle (monosynaptic) reflex. It assess the intactness of the sensory arm (Ia and Ib fibres) as well as the motor arm of the reflex (α motor neurons, sciatic nerve and tibial nerve). It is measured by starting with a submaximal stimulus which is later incremented at a constant rate. Initially M wave appears which slowly increases in size and later another wave called 'H' wave arises. 'H' wave slowly increases in size while 'M' wave decreases in size. Both the latency for getting 'H' wave and ratio of the amplitude of the largest 'H' wave to that of the largest M wave (H:M ratio) are calculated. It shows increased excitability of the spinal neurons post spinal cord injury which can be attributed to spasticity. But after the ejaculatory response, H reflex will show a transient reduction in the amplitude following which the amplitude increases for about 12 minutes.(47–50)

(VIb) F-wave (Foot wave) from tibial nerve evaluates the motor arm of the tibial nerve including the motor neurons, sciatic nerve and tibial nerve. It is an example of antidromic conduction which uses supramaximal stimuli. A train of 10 stimuli are given and 2 waves may arise according to the intactness. First wave is the M wave, a small wave which is about 5% of the M wave amplitude is called F wave. F wave if present shows the intactness of the motor arm.(51–54)

The somatic responses are the reflexes which occur during the penile vibrator stimulation. They are (i) abdominal contractions, (ii) piloerection, (iii) hip abduction, (iv) hip adduction, (v) muscular spasms in the lower limbs, and (vi) a composite movement of hip flexion, knee flexion and thigh abduction which simulates a withdrawal response.(36,43)

Patients with spinal cord injury do not have sensation below the level of injury. Hence, afferent inputs like vibratory stimulation along the dorsal penile nerve to the sacral segment can elicit ejaculation if spinal cord is preserved up-to T10 level. Thus, penile vibrator induced semen collection in men with SCI requires integrity of the spinal segments up-to T10 level.(10,35,36)

Semen collection in males with spinal cord injury is currently done using methods like penile vibrator stimulation and electroejaculation. Penile Vibrator Stimulation commonly called as PVS, is the most preferred method because of the ease of availability, less cost, patient preference, less time and expertise needed and as it is

non-invasive.(55–57)The stimulation is done with the help of specialised device called penile vibrator which is used to stimulate in the frenular aspect of the glans penis. The stimulation is done for 3-5 minutes with period of rest in between and the sequence is repeated for 2-3 times. High amplitude penile vibrators (>2.5mm) yield a better result of about 15-30% more than ones with low amplitude.(58) Two devices have been approved by the FDA for ejaculation in men with spinal cord injury, FERTI CARE personal® (Multicept, Denmark) and the VIBERECT® (Reflexonic, Frederick, MD, USA). These devices became commercially available in 1995 and in 2011 respectively. Parameters like amplitude and frequency can be modified in FERTI CARE personal® (Multicept, Denmark). Highest amplitude and frequency that can be reached with the device is 3.5mm and 100 Hz. It is designed in such a way that spinal injured persons with even poor hand functions (cylindrical grasp / mass grasp present) can operate the device. Viberect® has two vibrating surfaces that will stimulate the ventral and dorsal aspect of the glans penis simultaneously. It has a preset amplitude and frequency and it cannot be modified.(8,35,59–61)

Two penile vibrators can be used simultaneously with one on the dorsum and other over the frenulum of penis. It was found that this technique has a better ejaculatory efficacious than the use of a single vibrator.(62) Meanwhile electrical stimulation to the anterior wall of abdomen can also increase the incidence of the desired effect when used along with the use of PVS.(63,64) Using pharmacological agents like phosphodiesterase agents like Sildenafil / Vardenafil and adrenergic agonists agents like Midodrine has shown to increase the ejaculatory efficiency when used alongside PVS.(65,66) The average amount of viable and motile sperms in an ejaculate with

PVS is about 5 million which by itself is adequate for procedures to aid fertilization. In multiple studies, the success of semen collection with the use of PVS has been described at around 80% for patients with neurological level above T10 level and this reduce to about 20% in patients below T10 level.(67)

If trial of PVS fails, electroejaculation is used as a means to collect semen. Electroejaculation is done by electrically stimulating the seminal vesicles, prostrate and surrounding structures using a rectal probe which delivers electrical pulses with duration of 5 second with an interval of 20 seconds between successive stimuli and the cycle is then repeated. As there is chance of retrograde flow of semen into the urinary bladder, prior preparation of the bladder has to done before the procedure. This preparation facilitates semen collection in case of retrograde ejaculation. If collection of semen fails, the current impulse is increased by about 2V.(55,68)

Prostate massage is another option used for semen retrieval. The process is to guide the semen collected in the ampulla of vas deferens and seminal vesicles by massage therapy. Efficacy is lesser than PVS and electroejaculation. But in incomplete spinal cord injury, it has been tried in some countries and successful instances of fertilization has been reported.(69–71)

Pharmacotherapeutic agents have also been tried for inducing seminal expulsion by natural methods. Cholinesterase enzyme inhibitors like neostigmine and physostigmine have been found to be efficacious. Neostigmine has been given intrathecally while physostigmine has been given subcutaneously. However, these

drugs had potent side-effects like throbbing headache, nausea, vomiting, abdominal cramps, diarrhoea and even death due to brain hemorrhage. Their usage has therapeutically dropped because of poor patient preference and side effects. (72–74)

Oral midodrine, α1-adrenergic receptor agonist is currently used for treating hypotension among patients with SCI as it causes vasoconstriction. As opposed to the cholinesterase inhibitors, midodrine was thought to produce less side effects, because it more selective in its binding to the receptor. Midodrine when given intravenously or intramuscularly was used clinically for treating retrograde ejaculation. Encouraging results have been seen with oral midodrine in multiple studies. When used along with penile vibrator stimulation, the successful responses increased from 56% to 68% with use of midodrine. The main side effect is hypertension, hence blood pressure should be monitored in men with SCI. Autonomic dysreflexia can also occur in spinal cord injured persons with neurological level T6 or above during use of midodrine.(66,75–77).

Other method for semen collection is Surgical Semen Retrieval (SSR). It can be of two types, extraction and aspiration. Sperm can be extracted directly from testis by a process called TESE. Aspiration of sperm can be done by three methods namely direct sperm aspiration from testis (TESA), microepididymal method of sperm aspiration (MESA) and percutaneous epididymal aspiration (PESA). The viable and motile sperm count obtained following the procedure is low, obligating the need for artificial fertilization techniques like intrauterine insemination, in-vitro fertilization techniques, intra-cytoplasmic sperm injection (ICSI) and blastocyst transfer. These procedures are

expensive, hence, they are reserved for persons with spinal cord injury who have failed trials with both PVS and electroejaculator.(8,71,78–80)

In a retrospective study done recently among Asians, 46.15% of persons with complete spinal cord injury had successful response with Penile vibrator. Among the patients with lesion at T6 and above, the success rate was 66.7% and for lesions below T6 it was 33.3%.(81)

SUBJECTS and METHODS

Setting:

This study was conducted in Rehabilitation institute, Department of Physical medicine and rehabilitation, Christian Medical College, Vellore, Tamil Nadu.

The study was approved by the Research and Ethics committee of the Institutional Review Board, Christian Medical College, Vellore Ref: IRB Min. No. 10097 dated June 10th 2016 (Annexure-I).

Patients with spinal cord injury admitted in Rehabilitation Institute were recruited as the study population after a valid and informed consent was given. Sample collection began on first of July 2016 and the period of recruitment was from July 2016 to July 2017. The study did not involve follow up. The sample collection was started with the aim to achieve a sample size of 72 (36 with BCR +ve and 36 with BCR -ve).

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Participants:

Inclusion Criteria:

Patients with spinal cord injury with the following attributes were included:

1. T6 Neurological level or below, complete injury (ASIA A)

2. Age group 18 - 50 years

3. Duration since injury: more than six months

4. Patients who were willing to participate and gave a valid and informed consent.

Exclusion criteria:

Patients with spinal cord injury with the following attributes were excluded:

1. Neurological level above T6
2. Age <18 yr or >50yr.
3. Injury duration < 6 months.
4. Acute local inflammatory pathology
5. Patients with untreated hypertension or diabetes
6. Patients with a known cardiac disease
7. Patients with history of autonomic dysreflexia
8. Patient's with coexisting brain injury or psychiatric illness
9. On medications like anti-psychotics and ganglion blockers.

Source:

In-patients admitted under Department of Physical Medicine and Rehabilitation.

Method of case ascertainment: Male patients diagnosed with traumatic spinal cord injury with a neurological level above T6 were excluded to avoid the risk of autonomic dysreflexia.

Primary outcome**:**

- Response to penile vibratory stimulation.

Predictors of outcome**:**

i. Electrophysiolgical: F-wave from Tibial N stimulation; H-reflex from soleus.

ii. Clinical: Neurological level, superficial abdominal reflex, cremasteric reflex, bulbo-cavernous reflex, hip flexor response and ankle jerk.

Potential confounder / effect modifier**:** None

a) Response to penile vibratory stimulation was noted as present or absent. Two trials of stimulation each lasting for 5 minutes was given with a five minute rest period between trials. Since, the patient may not have sensation they may not report a successful response. Moreover, due to incoordination of internal and external urethral sphincter the semen often flows into the urinary bladder in a retrograde manner. Hence, catheterization of the bladder was done before and after the vibrator application and urine was examined for the presence of spermatozoa.

b) A Tibial F-wave was obtained by stimulation the nerve in the lower limb using an electrical stimulation of a very short duration and intensity being slightly

higher than that required to elicit a motor response in the muscles supplied by the nerve. Responses were recorded as present or absent. In addition, the latency was measured. Recording was done from both legs.

c) H-reflex from soleus (calf muscle) was obtained by stimulation of the tibial nerve with an electrical stimulus in the popliteal fossa. After cleaning the area, electrodes were placed over the soleus muscle. A stimulus of intensity lower than that required for eliciting a motor response was given. On stimulation, a H wave was obtained. The amplitude of the H wave increases with each increment in stimulus intensity. At a point, another wave called M wave starts appearing and increases in amplitude during this time, the amplitude of H wave starts reducing. Latency of peak H reflex and the HM transition time was measured. The test was done on both sides.(51,82)

d) Neurological level was determined by clinical examination, in accordance with standards as laid down by the American Spinal Injury Association (ASIA).

e) Clinical neurological examination (including hip flexor response, bulbocavernous reflex, cremasteric reflex, superficial abdominal reflex and ankle jerk) was done in accordance with current guidelines(44)

f) The hip flexion response is a pathological flexion reflex seen commonly in individuals with spinal cord injury. In these patients, firmly stroking the sole of

the foot (S1) elicits a hip flexion response demonstrating the integrity of spinal cord upto L2 segment.

g) The bulbocavernous reflex is tested by gently pressing the glans penis resulting in contraction of the anal sphincter. It tests integrity of the sacral spinal segments.

h) Cremasteric reflex is elicited by stroking the upper inner aspect of the thigh resulting in contraction of the cremasteric muscle. It tests integrity of L1 segment.

i) Superficial abdominal reflex is elicited by stroking skin over the anterior abdominal wall resulting in pulling of the umbilicus in the direction of the stimulus. Lower abdominal reflex tests integrity of T10-T12 segment.

j) Ankle jerk is elicited by striking the tendo-achilles with a reflex hammer resulting in contraction of the gastro-soleus muscles. It test integrity of S1 segment.(36,44)

Observer bias**:** was reduced as the same investigator (principal investigator) did the clinical neurological examination of every patient. In addition, the principal investigator performed objective electrophysiological tests and assessed response to penile vibratory stimulation.

SAMPLE SIZE & STATISTICS

Sample size:

Bulbocavernosus reflex (BCR) has been shown to be a good predictor for ejaculation. Specificity and sensitivity for the test is about 90%.(36) So with 10% error confidence interval, total sample size will be 72 (36 with BCR +ve and 36 with BCR -ve).

Statistics**:**

The individuals who have a successful response to penile vibratory stimulation will be classified as responders and those who do not have a response will be classified as non responders. Data will be compared between responders and non responders. Sensitivity and specificity will be calculated for each clinico electrophysiological test. We will also attempt to make a composite score by using combination of the tests.

METHODOLOGY

Persons with spinal cord injury who were admitted for rehabilitation under department of Physical Medicine and Rehabilitation were recruited for the study. Screening was done for inclusion and exclusion criteria as mentioned. A valid and an informed consent was obtained. Following this a detailed neurological assessment including hip flexor response, cremasteric reflex, bulbo-cavernosus response and ankle jerk were

done. Level of spinal injury was reassessed with the ASIA (American Spinal Injury Association) scale. Objective electrophysiological tests were done to elicit Tibial F-wave and Soleus H-reflex. Then a trial of penile vibratory stimulation was given which lasted for 5 minutes, followed by 5 minute rest. The cycle was repeated twice. Since the patients do not have sensation, they may not able to have a successful ejaculatory response. Moreover, due to atrophy and incoordination of internal and external sphincter musculature, semen can flow backwards into the urinary bladder. Hence, a sample from the bladder was taken by catheterization before and after the vibrator application and the urine samples were sent for examination under microscope for the presence of spermatozoa.

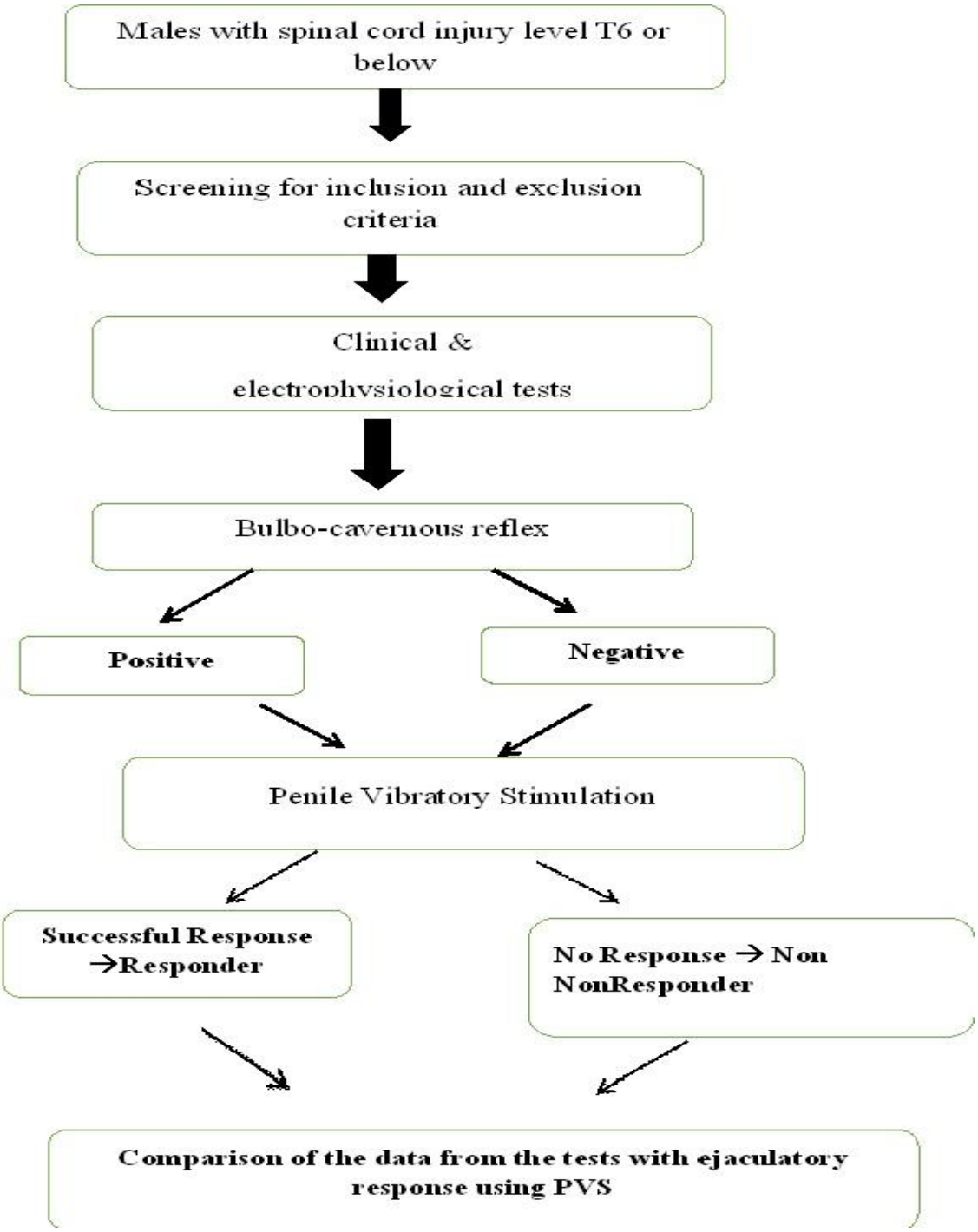
The individuals who had a successful response to penile vibratory stimulation were classified as responders and those who did not have any ejaculatory response were classified as non responders. Data obtained was compared between responders and non responders.

PENILE VIBRATOR STIMULATION

Patients were shifted from wheelchair to the bed where the clinical assessment takes place and they were positioned supine. During PVS, blood pressure was checked with an automated blood pressure monitoring device. In this study, we used high amplitude vibrator (FERTICARE personal, Multicept, Denmark). Stimulation was given for 5 min and then stopped for 5 min for avoiding a potential shear injury to the skin. The second trial was given for 5 minute of rest. The stimulation was stopped, once semen

was collected or if there was anejaculation in the presence of signs suggestive of sympathetic activation. The urine samples collected prior to and after the procedure, were sent to laboratory for microscopic analysis to look for presence of spermatozoa.

DETAILED DIAGRAMMATIC ALGORITHM



RESULTS

The penile vibrator used in the study is Ferticare personal ® penile vibrator at an amplitude of 3.5mm and frequency of 100 Hz since, the studies in the past had shown that higher amplitude vibrator has better outcomes with penile stimulation. (15)

AGE OF THE PARTICIPANTS IN THE STUDY.

Among the 23 participants in the study, mean age was 33.2 years with a standard deviation of 6.86 years. Among the persons with successful response to PVS (Responders), mean age was 34.14 years with standard deviation of 7.82 and persons with unsuccessful response to PVS (Nonresponders), mean age was 32.81 years with a standard deviation of 6.64.

Mean age of participants (years)	33.2
Standard deviation	6.86
Median age of participants (years)	28
Minimum age (years)	24
Maximum age (years)	47

Table (II) showing the mean and median age of participants in the study

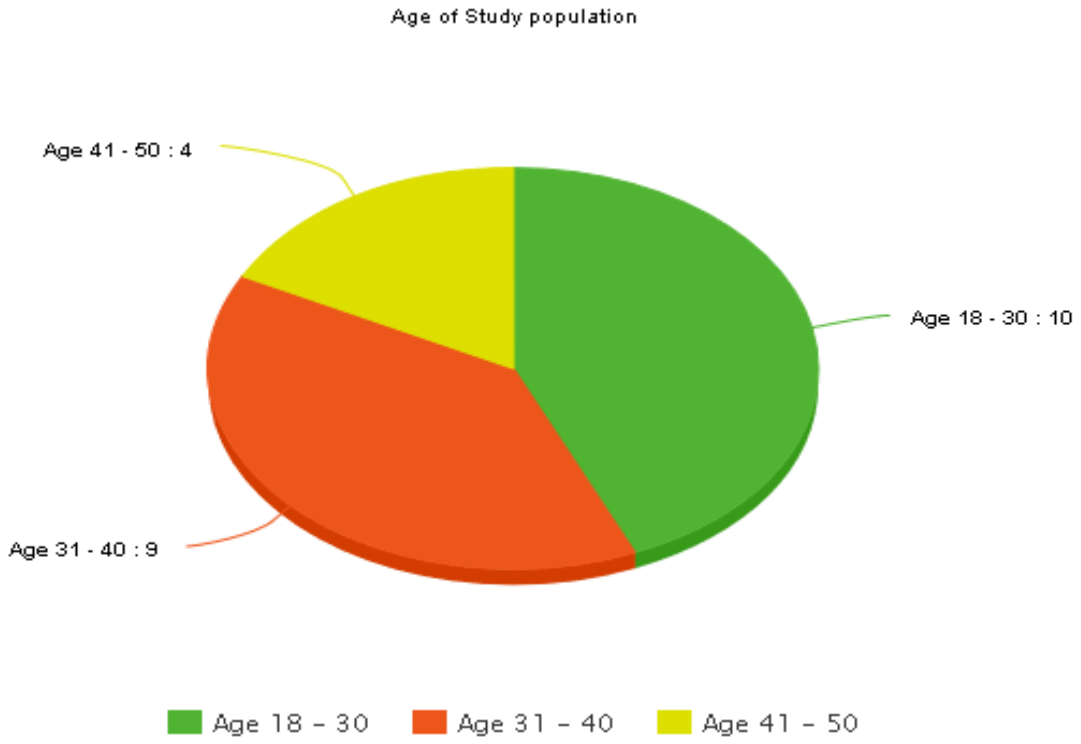


Figure (VII) Pie chart plotting the age of the participants of study.

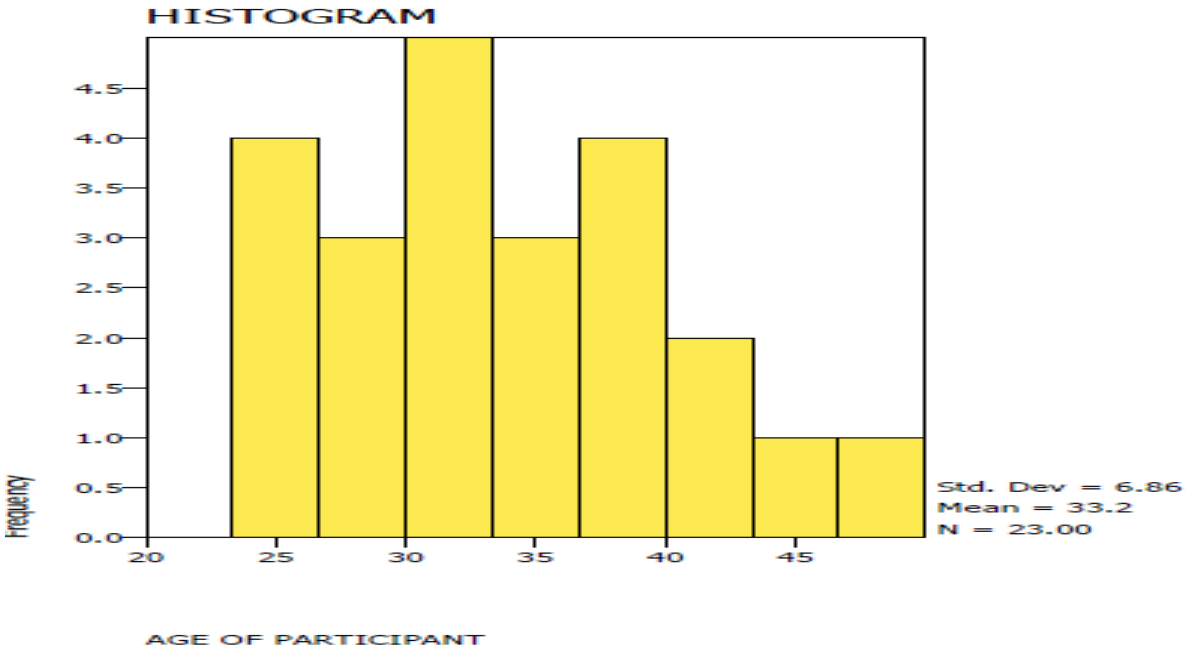


Figure (VIII) Bar graph plotting the age of patients participating in study

	Responders	Non responders
Mean age (years)	34.14	7.82
Standard deviation	32.81	6.64

Table (III) comparing the mean age (in years) between responders and non-responders.

MODE OF INJURY

Most common cause of spinal cord injury in those participated was fall from height which was followed by road traffic accidents.

Mode of injury	**Frequency**	**Percentage**
Fall from height	10	43.48
Road traffic accident	8	34.78
Fall after electrocution	4	17.39
Fall of heavy object on back	1	4.35

Table (IV) showing the frequency of mode of injury

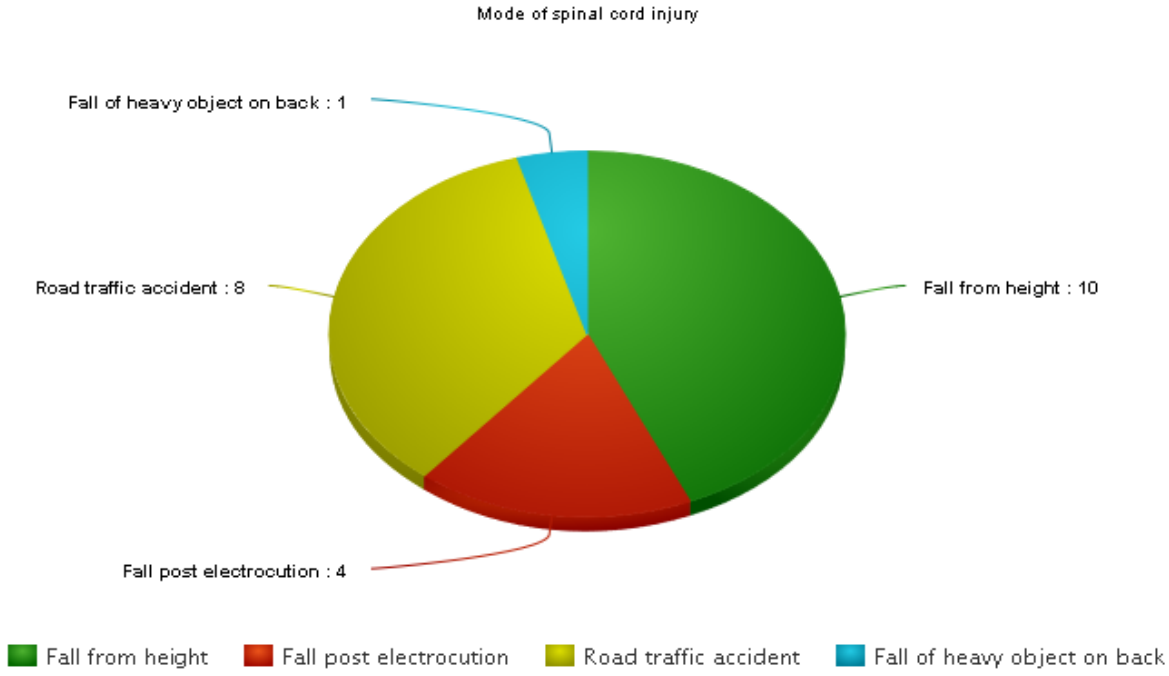


Figure (IX) Pie chart plotting the mode of injury

DURATION SINCE SPINAL CORD INJURY

Mean duration after the injury was 45 months with a standard deviation of 52 months. Maximum duration after the injury was 226 months and shortest duration was 6 months. In the responders, the mean duration was 34±28 months while in non-responders, it was 50±60 months.

Figure (X) pie chart plotting the duration of spinal cord injury

AGE AT THE TIME OF SPINAL CORD INJURY

The mean age at which the participants had spinal cord injury was 29 years with a standard deviation of 6.8 years.

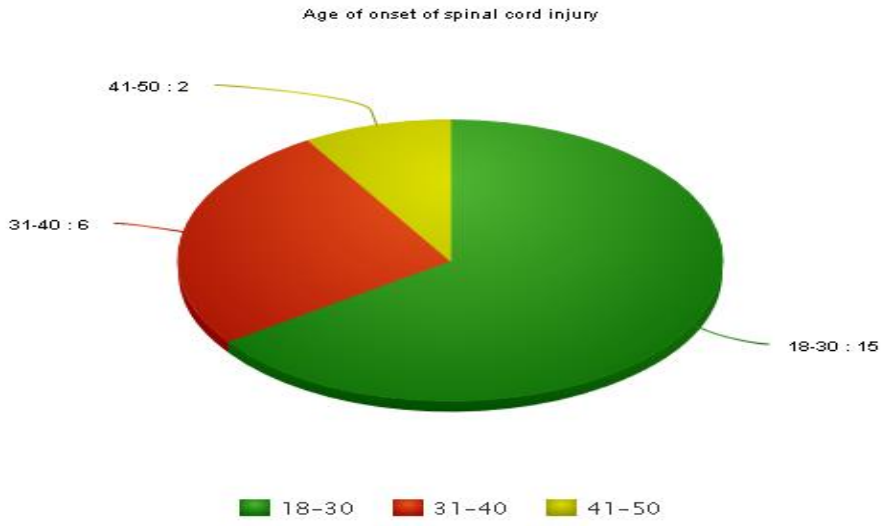


Figure (XI) pie chart plotting the age of onset of spinal cord injury

VERTEBRAL LEVEL OF SPINAL CORD INJURY

Based on the vertebral level of injury, 74%(n= 17) of the study population had T9 – T12 vertebral fractures while 13% (n=3) each of population had T6 – T8 and L1 –S1 vertebral injuries.

Vertebral level	Frequency	Percentage
T6-T8	3	13.04
T9-T12	19	73.91
L1 – S1	3	13.04

Table (V) showing the frequency of vertebral levels of participants

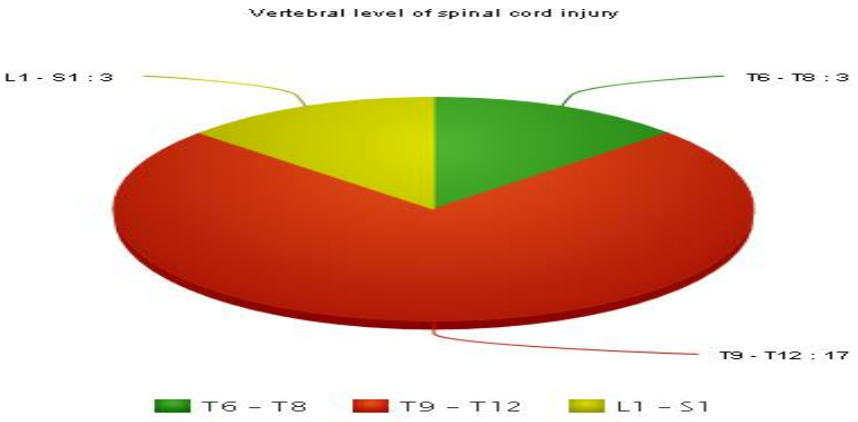


Figure (XII) pie chart plotting the vertebral level of spinal cord injury

Vertebral level	Responders with PVS	Non responders with PVS
T6-T8	3	0
T9-T12	2	15
L1 – S1	2	1
Total	7	16

Table (VI) comparing the vertebral levels between responders and non responders.

MARITAL STATUS AND NUMBER OF CHILDREN FOR THE PARTICIPANTS

Among those recruited, 15 were married and eight were unmarried. Six of the married couples had no children. While all the other nine couples had children before the spinal cord injury. 61 % (n=14) of the participants had no children.

	Frequency	Percentage
Married	15	65
Unmarried	8	35

Table (VII) showing the marital status of participants

No of children	Frequency	Percentage
0	14	61
1	2	9
More than 1	7	30

Table (VIII) showing the number of children for the participants.

Figure (XIII) Pie chart plotting the marital status of participants

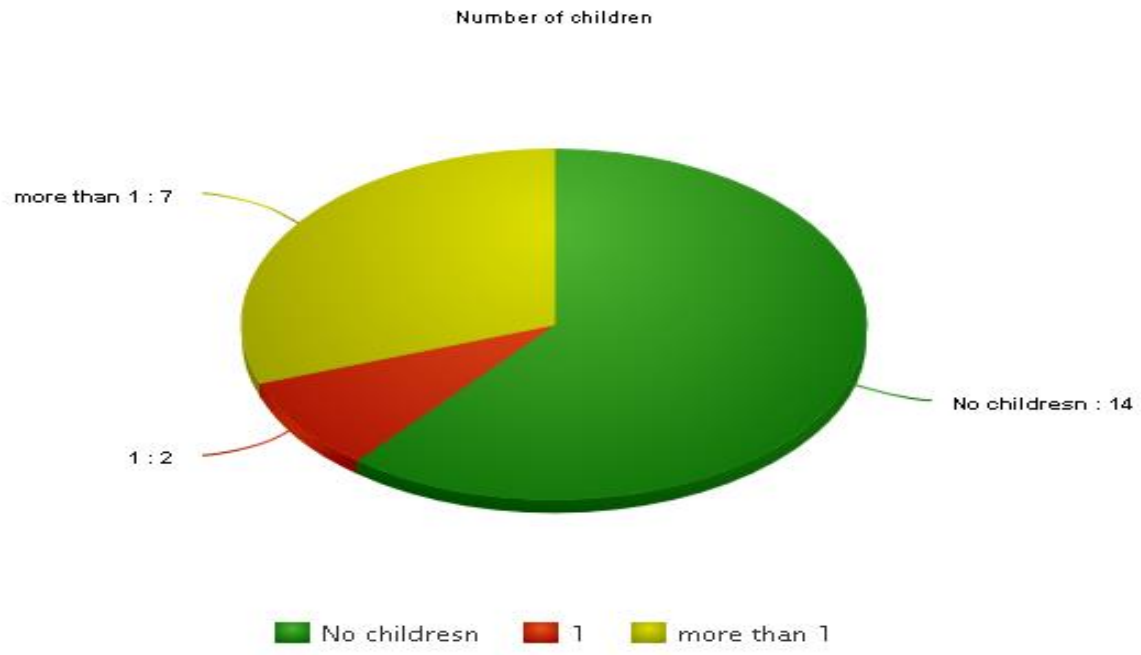


Figure (XIV) Pie chart plotting the number of children for the participants

NEUROLOGICAL LEVEL OF SPINAL CORD INJURY

Out of the 23 patients participated, four were having the neurological level of T6-T8 while 19 were having a neurological level of T9-T12. In those patients with T6-T8 neurological level, all were responders while in those with T9-T12, only three were responders. p- value was 0.004 which is significant by Fischers exact test.

Neurological level	Frequency	Percentage
T6-T8	4	17.4
T9-T12	19	82.6

Table (IX) showing the neurological levels of participants

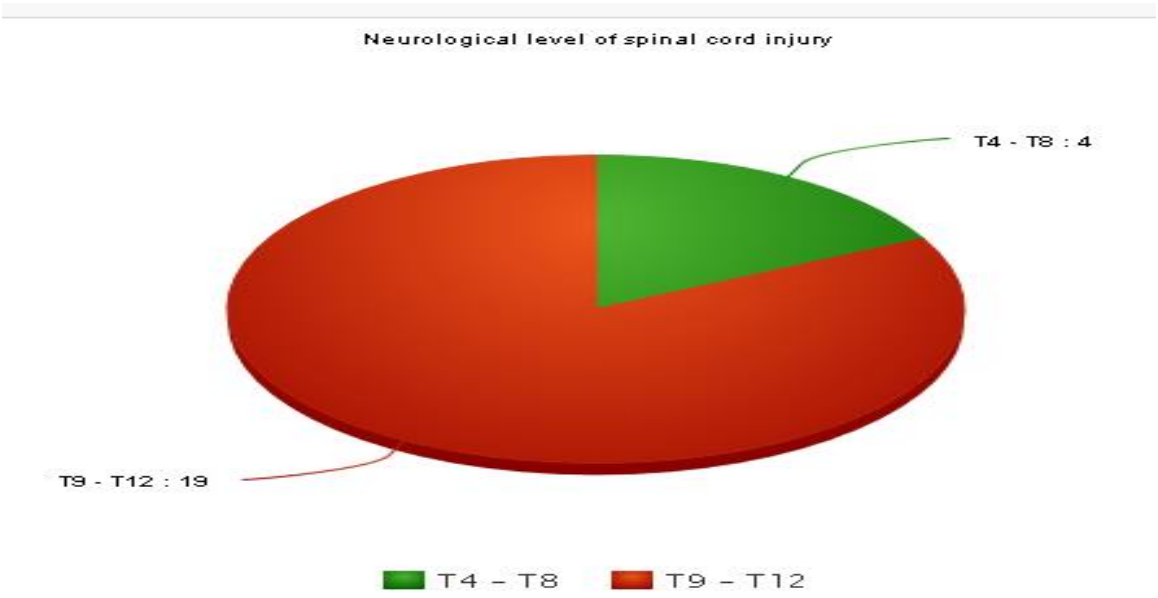


Figure (XV) Pie chart plotting the neurological level of spinal cord injury

Neurological level	Responders with PVS	Non responders with PVS
T6-T8	4	0
T9-T12	3	16
Total	7	16

Table (X) comparing the neurological levels between responders and non-responders.

SEXUAL FUNCTIONS REPORTED BEFORE SCI

All the participants of the study reported successful erections and seminal expulsions before sustaining spinal cord injury.

Sexual functions reported before SCI	Frequency of participants	Percentage
Erection	23	100
Ejaculation	23	100

Table (XI) showing the sexual functions before SCI

SEXUAL FUNCTIONS REPORTED AFTER SCI

82.6 %(n=19) participants reported erections and 26 %(n=6) reported successful ejaculatory response by natural methods post spinal cord injury . But about 65% (n=15) had reported whitish discharge in urine post spinal cord injury.

Sexual functions reported post SCI	Frequency of participants	Percentage
Erection	19	82.6
Successful ejaculatory response to Natural methods	6	26
Whitish discharge in urine	15	65

Table (XII) showing the sexual functions after SCI

SEXUAL FUNCTIONS REPORTED POST SCI VS PVS REPONSE

50% (n=3) of those who reported successful ejaculatory response with natural methods had successful response with PVS while about 33% (n=5) of those who noted whitish discharge in urine were able to have successful response with PVS. But there was no statistical significance between those who reported successful response to natural methods and their response with PVS.(p value 0.31)

Sexual functions after spinal cord injury	Responders with PVS	Non responders with PVS
In those with successful response to self Stimulation	3	3
whitish discharge in urine	5	10

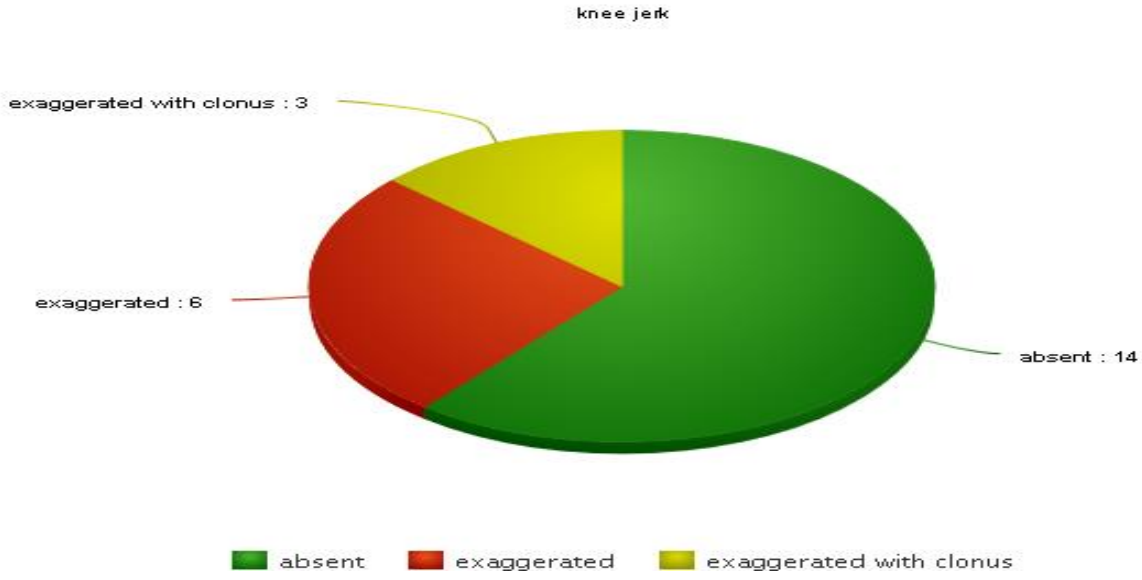
Table (XIII) comparing the previous sexual history between responders and non-responders.

KNEE JERK SENSITIVITY SPECIFICITY, KNEE JERK VS PVS RESPONSE

Among the participants, the knee jerk responses were absent in 60.87% (n=14), exaggerated in 39.13% (n=9) patients. Of those with knee jerk exaggerated, 33% (n=3) had successful responses with PVS . Sensitivity for knee jerk in predicting successful response with PVS is 42% while the specificity is 62%. (p value 0.318)

Knee jerk	Frequency	Percentage
Absent	14	61
Exaggerated	9	39

Table (XIV) showing the frequency of Knee jerk response in participants



Pie chart (XVI) plotting the incidence of knee jerk among participants

Knee Jerk	Response to PVS			Sensitivity	Specificity
	Yes	No	Total		
Present	3	6	9	42	62
Absent	4	10	14		
Total	7	16	23		

Table (XV) showing sensitivity, specificity, and comparison of knee jerk vs PVS response

LOWER ABDOMINAL SENSATION SENSITIVITY AND SPECIFICITY VS PVS RESPONSE

In patients with preserved lower abdominal sensations (T10-12), only 3 patients were able to have a successful response to PVS. Sensitivity and specificity for the same are 42% and 68.75% respectively. P value was calculated with Pearson chi square test and was found as 0.591 which is insignificant.

Lower abdominal sensation	**Response to PVS**			**Sensitivity**	**Specificity**
	Yes	**No**	**Total**		
Present	3	5	8	42	68.75
Absent	4	11	15		
Total	7	16	23		

Table (XVI) showing sensitivity, specificity, and comparison of lower abdominal sensation vs PVS response

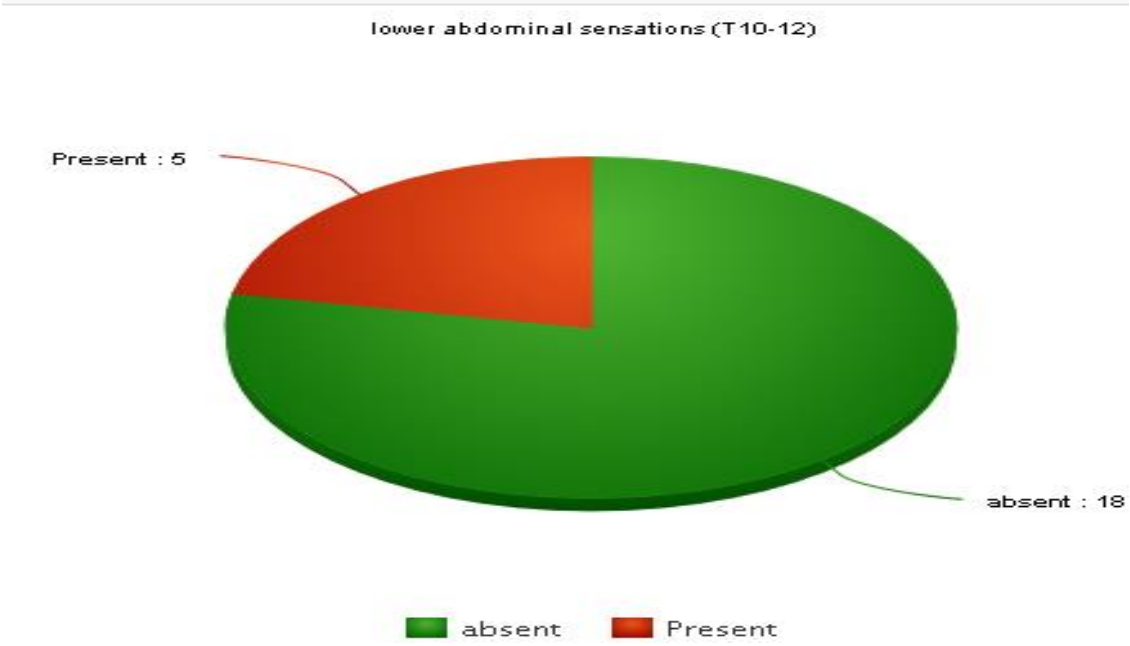


Figure (XVII) Pie chart plotting the incidence of lower abdominal sensation among participants

ANKLE JERK SENSITIVITY AND SPECIFICITY, ANKLE JERK VS PVS RESPONSE

Among the participants, the ankle jerk responses were absent in 69.6 % (n=16), exaggerated in 13% (n=3) and exaggerated with clonus in 17.4% (n=4) patients. Of those with ankle jerk present, 28%(n=2) were able to have successful responses with PVS. Sensitivity for ankle jerk in predicting successful response with PVS is 28% while the specificity is 68.75%. P value is 0.963 which is insignificant.

Ankle Jerk	Response to PVS			Sensitivity	Specificity
	Yes	No	Total		
Present	2	5	7	28	68.75
Absent	5	11	14		
Total	7	16	23		

Table (XVI1) showing sensitivity, specificity, and comparison of ankle jerk vs PVS response

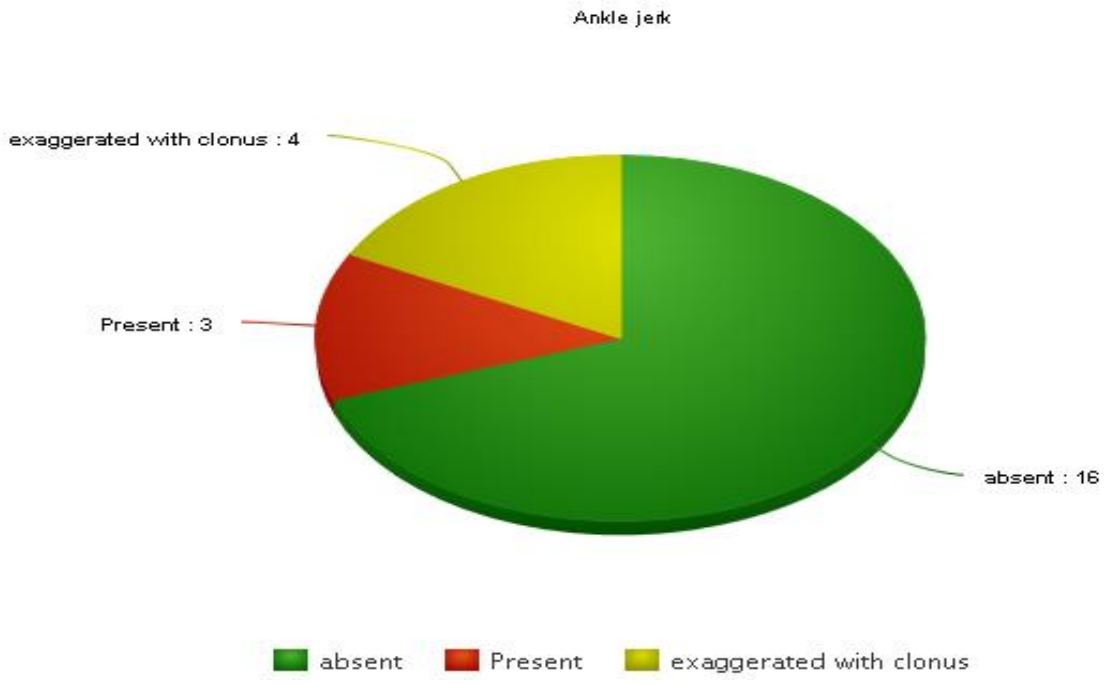


Figure (XVIII) Pie chart plotting the incidence of ankle jerk among participants

LOWER ABDOMINAL REFLEX (LAR) SENSITIVITY AND SPECIFICITY, LAR VS PVS RESPONSE

Among the participants, the lower abdominal superficial reflexes were present in 34.8% (n=8), patients. In those present, 37% (n=3) were able to have successful responses with PVS. Sensitivity in predicting successful response with PVS is 42% while the specificity is 68.75%. p value was .660 which is insignificant.

Lower Abdominal reflex	**Response to PVS**			**Sensitivity**	**Specificity**
	Yes	**No**	**Total**		
Present	3	5	8	42	68.75
Absent	4	11	15		
Total	7	16	23		

Table (XVIII) showing sensitivity, specificity, and comparison of lower abdominal reflex vs PVS response

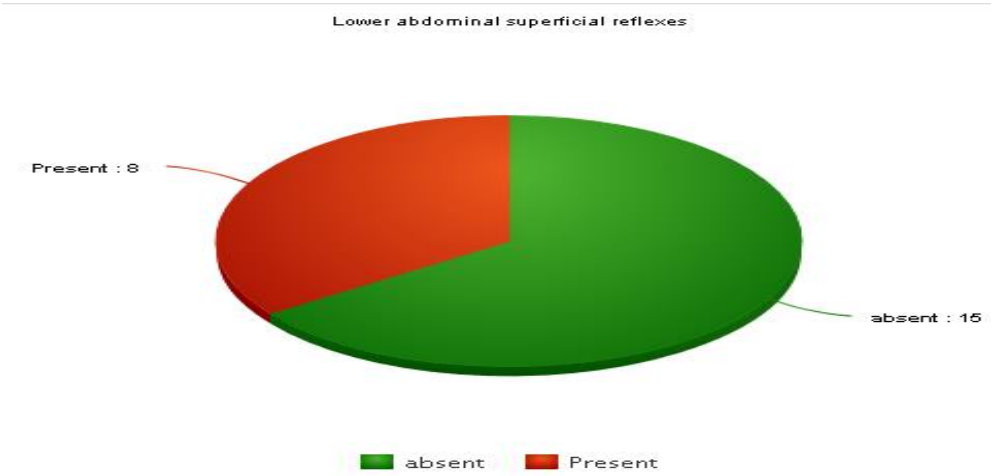


Figure (XIX) Pie chart plotting the incidence of superficial abdominal reflexes among participants

PLANTAR REFLEX (PR) SENSITIVITY SPECIFICITY, PR VS PVS RESPONSE.

Among the participants, the plantar reflexes were absent in 60.3 % (n=14), and exaggerated in 39.7% (n=9) patients. Of those with plantar reflex present, 42% (n=3) were able to have successful responses with PVS. Sensitivity for ankle jerk in predicting successful response with PVS is 42% while the specificity is 62.4%. P value is 1.001 which is insignificant.

Plantar Reflex	Response to PVS			Sensitivity	Specificity
	Yes	No	Total		
Present	3	6	9	42	62.4
Absent	4	10	15		
Total	7	16	23		

Table (XIX) showing sensitivity, specificity, and comparison of plantar reflex vs PVS response

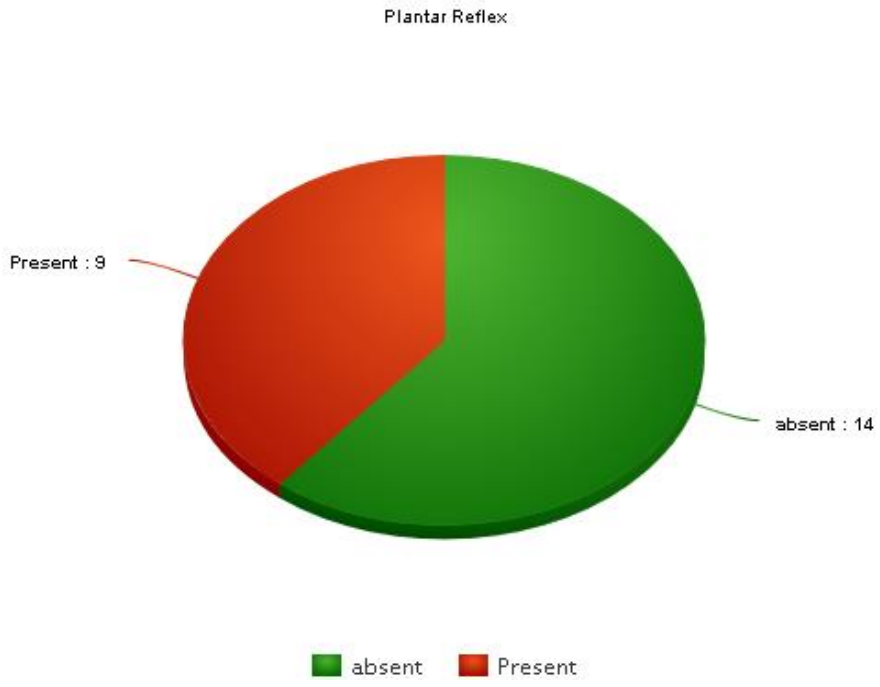


Figure (XX) Pie chart plotting the incidence of plantar reflex among participants

HIP FLEXOR RESPONSE SENSITIVITY SPECIFICITY, HFR VS PVS RESPONSE

The hip flexor responses were present in 30.4% (n=7). Of those with hip flexor responses present, 28% (n=2) was able to have successful responses with PVS. Sensitivity in predicting successful response with PVS is 28% while the specificity is 68.75%. P Value is 1.000 and is insignificant

Hip Flexor response	**Response to PVS**			**Sensitivity**	**Specificity**
	Yes	**No**	**Total**		
Present	2	5	7	28	68.75
Absent	5	11	15		
Total	7	16	23		

Table (XX) showing sensitivity, specificity, and comparison of hip flexor response vs PVS response.

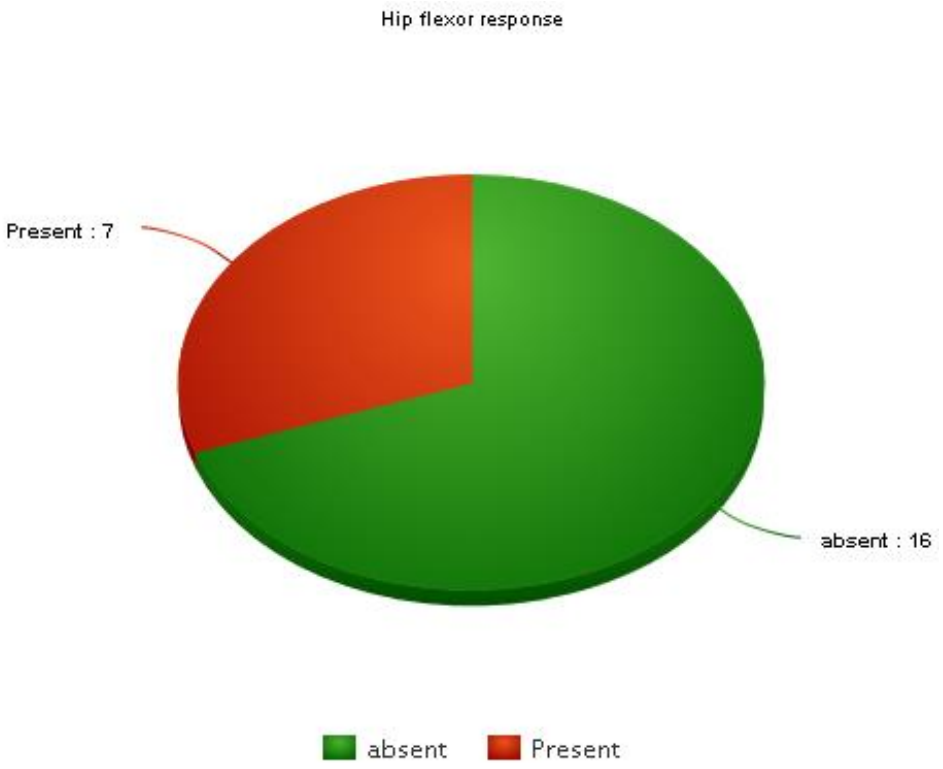


Figure (XXI) Pie chart plotting the incidence of hip flexor response among participants

KNEE FLEXOR RESPONSE SENSITIVITY SPECIFICITY, KFR VS PVS RESPONSE

The knee flexor responses were present in 30.4% (n=7). Of those with knee flexor responses present, 28% (n=2) were able to have successful responses with PVS. Sensitivity for ankle jerk in predicting successful response with PVS is 28% while the specificity is 68.75%. P value is 1.000 and is insignificant.

Knee Flexor response	Response to PVS			Sensitivity	Specificity
	Yes	No	Total		
Present	2	5	7	28	68.75
Absent	5	11	15		
Total	7	16	23		

Table (XXI) showing sensitivity, specificity, and comparison of knee flexor response vs PVS response.

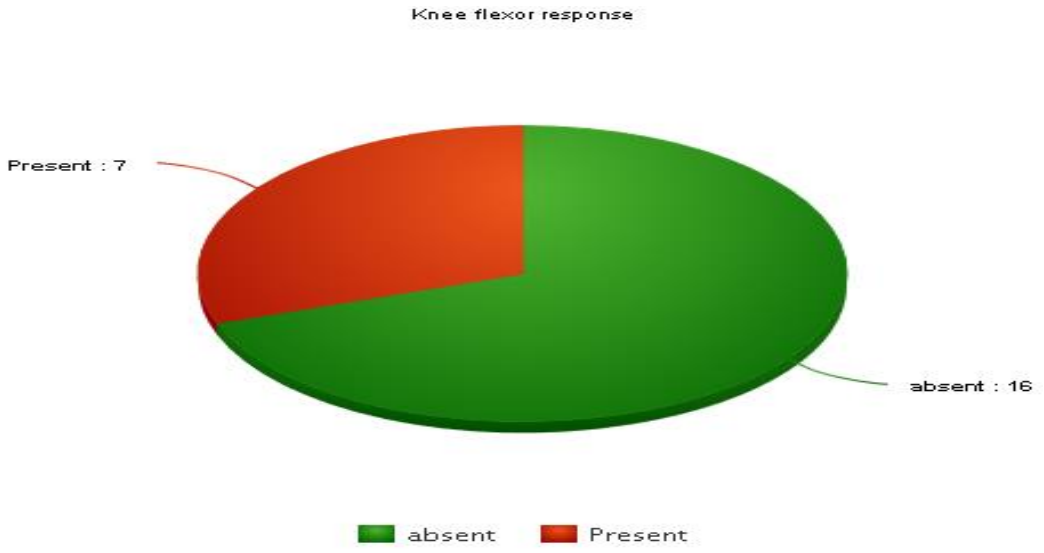


Figure (XXII) Pie chart plotting the incidence of knee flexor response among participants

CREMASTERIC REFLEX

Among the participants, the cremasteric reflexes were absent in all patients.

BULBOCAVERNOUS REFLEX (BCR) SENSITIVITY SPECIFICITY BCR VS PVS RESPONSE

Among the participants, Bulbocavernosus reflexes (BCR) were present in 65.2 % (n=15), patients. In those present, 71.5% (n=5) were able to have successful responses with PVS. Sensitivity in predicting successful response with PVS is 71.5% while the specificity is 37.2%. P value is 1.000 and is insignificant.

Bulbo-cavernous Reflex	**Response to PVS**			**Sensitivity**	**Specificity**
	Yes	**No**	**Total**		
Present	5	10	15	71.5	37.2
Absent	2	6	8		
Total	7	16	23		

Table (XXII) showing sensitivity, specificity, and comparison of bulbocavernous reflex vs PVS response.

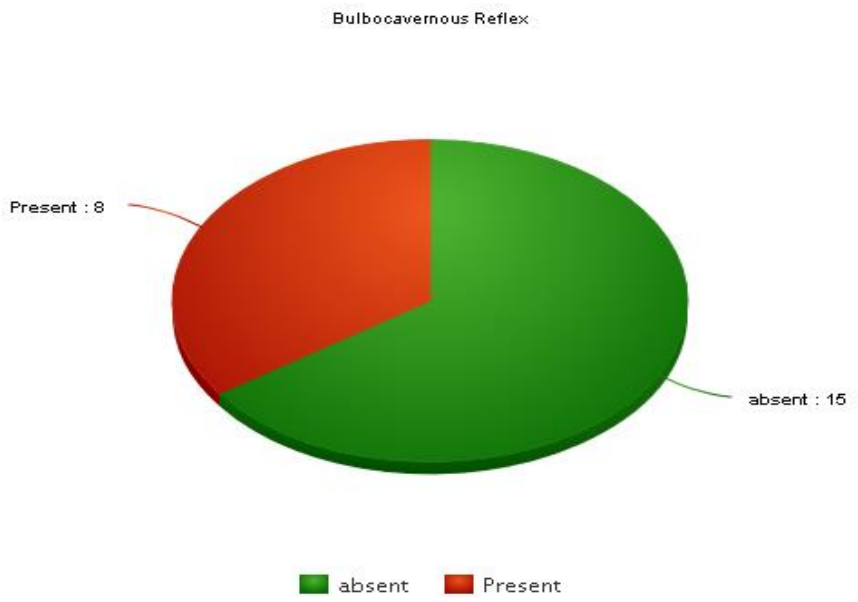


Figure (XXIII) Pie chart plotting the incidence of bulbocavernous reflex among participants

SOLEUS H REFLEX (SHR) SENSITIVITY SPECIFICITY SHR VS PVS RESPONSE

Soleus H reflex was present in 7 of the 18 patients (30.8%) in whom the study was done. The sensitivity of Soleus H reflex is 28% and specificity is 54%.

Soleus H Reflex	**Response to PVS**			**Sensitivity**	**Specificity**
	Yes	**No**	**Total**		
Present	2	5	7	28	54
Absent	5	6	11		
Total	7	11	18		

Table (XXIII) showing sensitivity, specificity, and comparison of Soleus H reflex vs PVS response

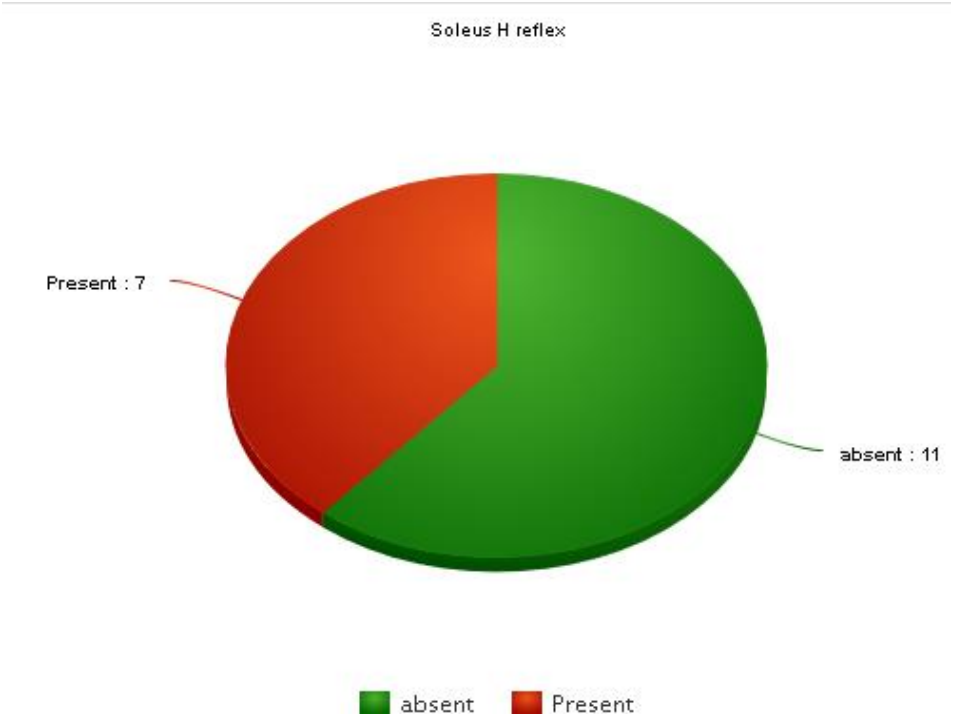


Figure (XXIV) Pie chart plotting the incidence of Soleus H reflex among participants

POSTERIOR TIBIAL F WAVE (PTF WAVE) SENSITIVITY AND SPECIFICITY, PTF WAVE VS PVS RESPONSE

Posterior tibial F wave was present in 7 of the 18 patients (30.8%) in whom the study was done. The sensitivity of Posterior tibial F wave is 28% and specificity is 54%.

Posterior tibial F wave	Response to PVS			Sensitivity	Specificity
	Yes	No	Total		
Present	2	5	7	28	54
Absent	5	6	11		
Total	7	11	18		

Table (XXIV) showing sensitivity, specificity, and comparison of Posterior tibial F wave vs PVS response

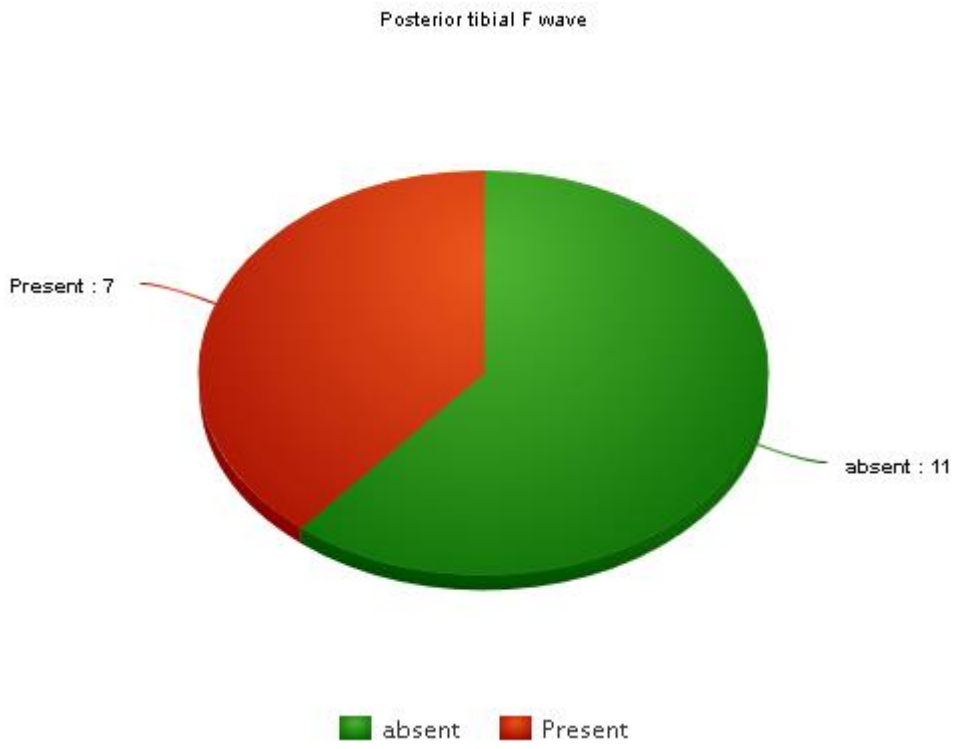


Figure (XXV) Pie chart plotting the incidence of Posterior tibial F wave among participants

SOMATIC RESPONSES SENSITIVITY SPECIFICITY PR VS PVS RESPONSE

Somatic responses were present in 47.3% (n=11) patients. 6 out of the 11 patients (54%) were able to have successful response with PVS. The sensitivity and specificity of somatic responses are 84% and 68.2% respectively. (P value 1. 001). Among the somatic responses, abdominal contractions were seen in about 36% patients(n=4). Both hip flexor and abdominal contractions were seen in 18% patients (n=2). In patients with successful response, hip flexion response was noted in 3 patients (42.9%) and paresthesia over the sole was noted in one patient(14.3%).

Somatic Responses	**Response to PVS**			**Sensitivity**	**Specificity**
	Yes	**No**	**Total**		
Present	6	5	11	84	68.2
Absent	1	11	12		
Total	7	16	23		

Table (XXV) showing sensitivity, specificity and comparison of somatic responses vs PVS response

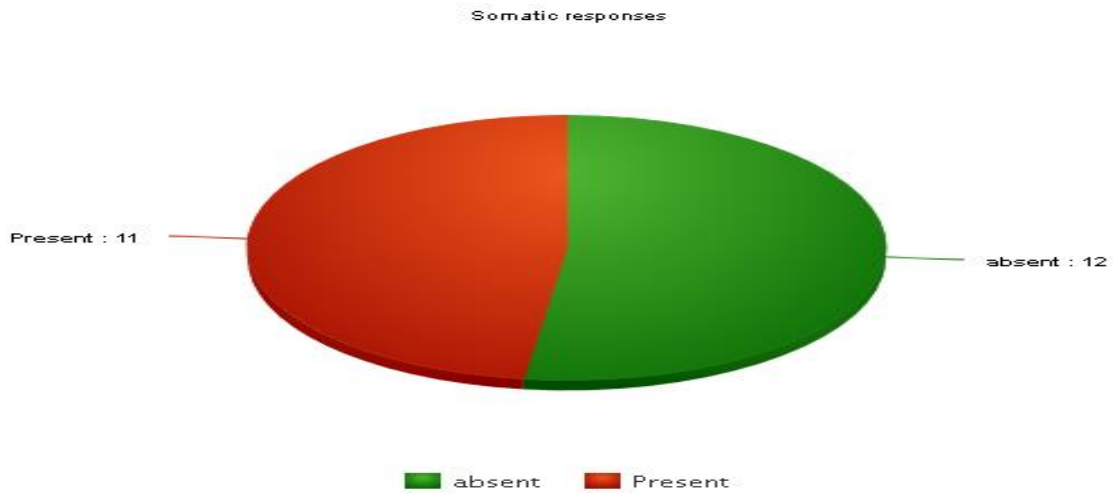


Figure (XXVI) Pie chart plotting the incidence of Somatic responses among participants

Somatic responses	Responders	Non responders
Abdominal contraction alone	2(28%)	1
Hip flexion alone	1(14%)	2
Hip adduction	0	1
Abdominal contraction with hip flexion	2(28%)	0
Paresthesia over sole of foot	1(14%)	1
No responses	1(14%)	11

Table (XXVI) showing comparison of types of somatic responses vs PVS response

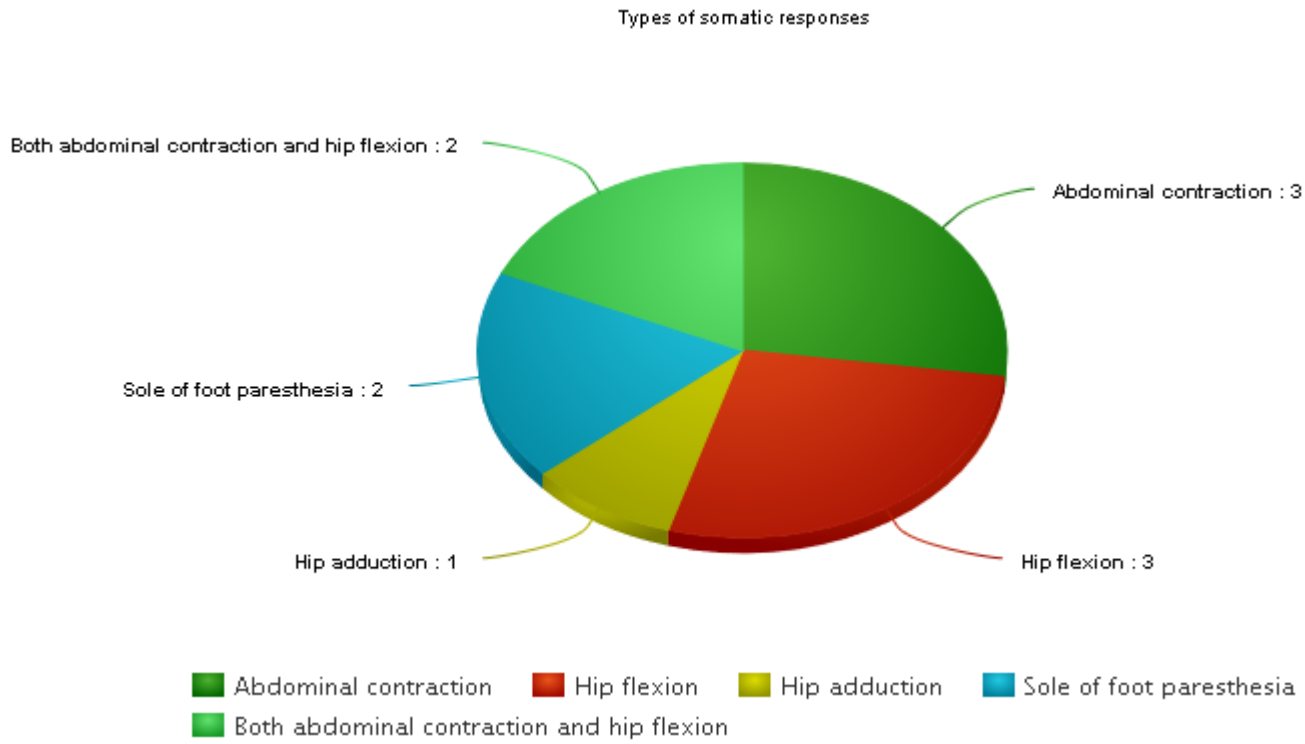


Figure (XXVII) Pie chart plotting the incidence of types Somatic responses among participants

PVS SUCCESS FREQUENCY IN TRIALS

In persons who had successful response with penile vibrator, only 30%(n=2) had both trials successful while other 71%(n=5) had only one trial successful.

PVS TRIAL	Success frequency
First trial	4
Second trial	1
Both trial success	2

Table (XXVII) showing comparison of successful PVS response frequency in trials

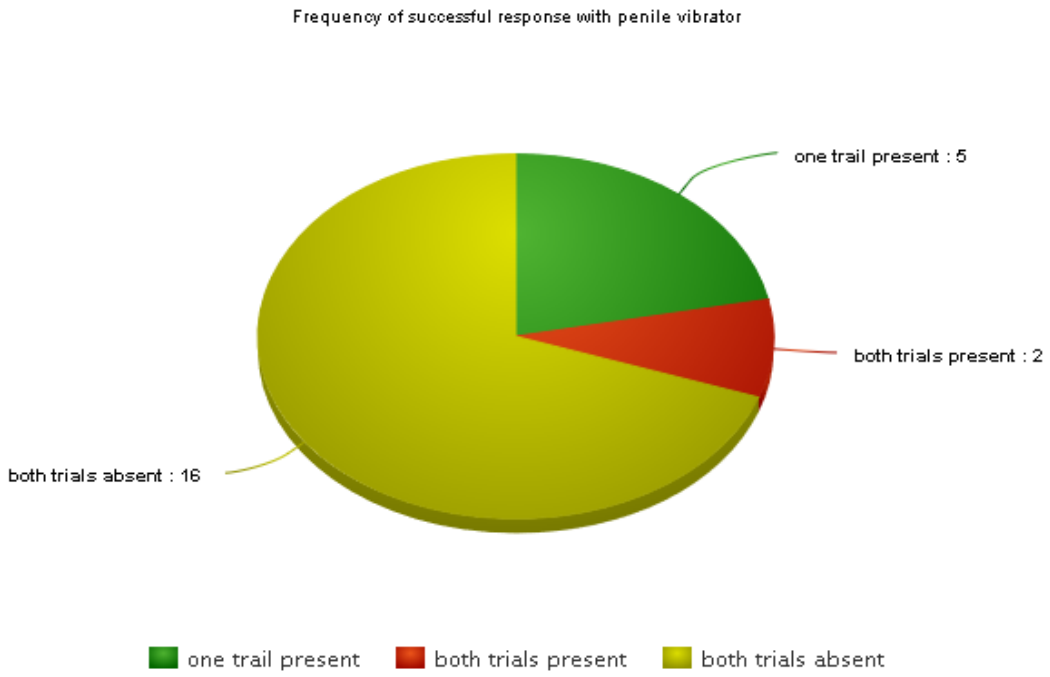


Figure (XXVIII) Pie chart plotting the incidence of success rate of trials with PVS among participants

URINE MICROSCOPY

Urine microscopy for spermatozoa in urine sample was only positive in one case. In that patient both the samples (pre and post exposure to PVS) showed spermatozoa.

PRESENCE OR ABSENCE OF BCR & HFR VS RESPONSE TO PVS

The most common reflex pattern seen among the participants of study was

(i) bulbocavernous reflex(BCR) positive and hip flexor response (HFR) negative (n=8) and

(ii) both bulbocavernous reflex and hip flexor response negative (n=8)

Reflex Patterns of BCR & HFR	Response to PVS		
	Yes	**No**	**Total**
BCR+ & HFR+	2	5	7
BCR + & HFR-	3	5	8
BCR – & HFR+	0	0	0
BCR- & HFR-	2	6	8
Total	7	16	23

Table (XXVIII) showing comparison between incidence patterns of BCR & HFR vs PVS response

SENSITIVITY AND SPECIFICITY OF THE COMBINED BCR AND HFR

Sensitivity and specificity of predicting successful response for reflex pattern with (i) both bulbocavernous reflex and hip flexor response positive are 28% & 31.3%,

(ii) bulbocavernous reflex(BCR) positive and hip flexor response (HFR) negative are 42% & 31.3%,

(iii) both bulbocavernous reflex and hip flexor response negative are 28% & 37.4% respectively

Reflex pattern	**Sensitivity**	**Specificity**
BCR + & HFR+	28	31.3
BCR+ & HFR –	42	31.3
BCR – & HFR –	28	37.4

Table (XXIX) showing Sensitivity and specificity of the combined BCR and HFR pattern

COMBINED BCR & HFR VS NEUROLOGICAL LEVEL

Neurological level	**Responders Percentage**	**BCR+ HFR + (No of responders / No of person with reflex pattern)**	**BCR + HFR – (No of responders / No of person with reflex pattern)**	**BCR – HFR + (No of responders / No of person with reflex pattern)**	**BCR- HFR- (No of responders / No of person with reflex pattern)**
T6 – T8	100 (n=4)	2/2 (100)	2/2(100)	0	0
T9 – T12	15.8(n=19)	0/5	1/6 (16.8)	0	2/8

Table (XXX) showing comparison between incidence patterns of BCR & HFR vs neurological level

DISCUSSION

Our study was designed to assess whether ejaculatory response to penile vibratory stimulation can be predicted with clinical and electrophysiological studies. A total of 23 patients were recruited in the study from first of July 2016 to July 2017 who satisfied the inclusion criteria and were willing to give their informed consent towards participation in the study. We recruited about 23 patients who were of the mean age 33 years (SD 6.8) and mean duration of injury 45 months (SD 52 months). Most common cause of spinal cord injury in this population was fall from height followed by road traffic accidents. Injury occurred at a mean age of 29 years with SD of six years. There was no statistically significant difference in the age groups and mean duration of cord injury between responders and non- responders with PVS. About 14 of the 23 patients had no children and 6 of them were married. Most of the participants in the study were having the vertebral level of injury T9 – T12 (n=17) while T6 – T8 and L1 – S1 had three each. All between T6 –T8 (n=3) vertebral level and two persons each from the other two group of vertebral levels were responders.

All the four spinal cord injured with the higher level (T6 –T8) who participated (n =4) in the study were responders and had a efficacy ratio of 100%. Meanwhile among rest of the participatins (n =19) in the study with lower level injury (T9 –T12), the efficacy ratio dropped to 15.8%. However both were found to be statistically significant (p value = 0.004). This signifies that the presence of intact lumbo-thoracic (T10 – L2)

and sacral (S2 –S4) centres along with intact neural pathways has a higher chance of getting better response with penile vibratory stimulation.

In a single centre study in Miami among spinal cord injured patients for 18 years, T10 and above was having an efficacy of about 60 % with PVS. But it dropped to about 21% in patients with neurological level T11 and below. Hence they attributed the result to the intactness of the spinal segment from T10 to S4.(42) In a study review done in Belgium with data available through research from 1973 to 2008, postulated that intactness of the spinal autonomic centres and their circuits are very important in having a successful response in penile vibratory stimulation. (10) In another study in Miami, overall success rate with penile vibrator for patients with neurological levels C2-C8, T1 ± T6, and T7 ± T12 were 71%, 73%, and 35%, respectively.(36) In a retrospective study done in Malaysia (n = 13), the successful responders were about 46% of the study population. Responders constituted about 66 % above neurological level of T6 and 35% for those below T6. (81)

Bulbocavernous reflex (S2,3,4), was present in about 72 percent (n=5) of the responders and 64 percent (n=15) of study population. Four of them had T6 –T8 neurological level. With the limitation of small sample, the results were not statistically significant. Even though the sacral segments being not intact in eight of the participants, about two of them were able to have a successful response. In the previous literature, it has been postulated that it is because of the sparing of the human spinal pattern generator segment.(26) But in those who were BCR negative and responders, the clinical reflexes were all absent.

The spinal ejaculation pattern generator (L3 – L5) which when preserved will help in initiating the ejaculatory reflex and orchestrating sympathetic, parasympathetic and somatic centres.(26) The clinical reflexes which can be used for assessing the intactness of the same are knee jerk (L2,**3**, 4), knee flexor response (L3 – S1) and Hip flexor response (L2–S1). Even though the knee jerk was present in nine of the participants, only three were responders. Knee flexor response and hip flexor response was noted in seven patients of which only two were responders. But there was no statistically significant correlation between intactness of L3,4,5 segments with penile vibrator assisted semen expulsion.

In our study we found that in participants with both BCR and HFR positive, only 28% were able to have successful response. In BCR and HFR negative participants, 25% were having a successful response. This was unlike the study done in Miami where four out five patients with positive BCR and HFR had positive response with PVS. Only 8% participants with both BCR and HR negative had positive response to PVS(36).

Electrophysiological reflexes like Soleus H reflex and Tibial F wave (S1) even though present in about 30% patients were only able to predict successful response in 28% (n=2) of the responders and was statistically insignificant. It shows that intactness of S1 spinal segment has no significant role in the ejaculatory pathway.

Somatic responses that were found in the study was abdominal contraction, hip flexion, hip adduction and paraesthesia over the dorsum of the foot. Withdrawal response, piloerection and extremity spasms were not noted as in the study in Miami. (36) Even though the responses were found in 47.3% (n=11) patients, six (54%) of them had successful response with PVS. Somatic responses were seen more in responders than in non responders. Sensitivity of the somatic responses was 84% but it was statistically insignificant. In those participants with abdominal contraction as response to penile vibration (n=5), four were able to have successful response. While in those with hip flexion response (n=5), only three were responders. In those patients with paraesthesia of foot (n=2), one participant was able to have successful response. In participants with both hip flexion and abdominal contraction responses, all were responders. Hence somatic responses like abdominal contraction and hip flexion if present then the chances of having a successful response with penile vibrator is high.

CONCLUSION

Neurological level of injury was more predictive index in assessment of fertility with PVS than any of the other reflexes (P= 0.004). Hence while contemplating on ideal candidates for use of PVS, neurological level of injury should be considered.

Bulbocavernous reflex (BCR) has a sensitivity of 72 % but specificity was about 50%. BCR still can be used as a screening tool to predict better responses with PVS. Since hip flexor response (HFR), cremasteric response and other clinical responses were having low specificity, so they cannot be used as a screening tool.

Even though some retrospective studies have proven the existence of spinal ejaculation pattern generator in L3 - L5 levels, there was no significant improvement in the responses when the clinical reflexes corresponding to those levels were present which was suggestive of intact reflex arcs.

Abdominal contractions and hip flexion responses if observed during penile vibration, are better predictors of ejaculation.

Electrophysiological indices were able to predict correctly in only two patients (responders) even though being present in seven participants. Hence they are not realistic predictors for successful response with PVS.

LIMITATIONS

Limitations of the study were:

(i) Low sample size

We could only recruit 23 patients of which, bulbocavernous reflex was present in 18 patients and in the rest it was absent. Collecting at least 36 patients in each group (BCR positive and negative) would probably have added to the significance.

(ii) Short study period

Study was started in September first 2016 and data collection was completed by first week of August 2017. As the topic was of a sensitive

nature and confidential, recruiting patients was not easy. Young males (≤ 24 years) were not willing to discuss the issue. Most of the spinal cord injured who presented had sustained the injury within 6 months, hence, they were excluded from the study.

(iii) Electrodiagnostic studies could not be completed in 5 participants due to unforeseen technical reasons.

RECOMMENDATION & FUTURE RESEARCH

- A study with larger sample size with addition of patients with neurological level above T6 would be recommended .
- In previous studies, the focus was mostly on lesions above T10 neurological level of injury. In this study, two of the persons whom were Bulbocavernous reflex (BCR) negative were able to have successful ejaculatory response with PVS . Hence the study can be extended to cauda equina patients in whom BCR is negative, which may add further insight about how these patients may have a successful ejaculatory response.
- In this study we used the Ferticare personal® vibrator which is a high amplitude vibrator with adjustable parameters but the main disadvantage with the same is that it is costly. The alternative is Viberect® which is a high amplitude vibrator with non adjustable parameters but it is comparatively cheap. The efficacy of these two vibrators can also be subjected to testing.
- Literature suggest that PVS efficacy can be increased by dual stimulation, giving electrical stimulation to the anterior abdominal wall or using pharmacologic agents like Midodrine. These techniques also can be subjected to further research.

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ANNEXURE

ANNEXURE-I

INSTITUTIONAL REVIEW BOARD ACCEPTANCE LETTER WITH QUERIES

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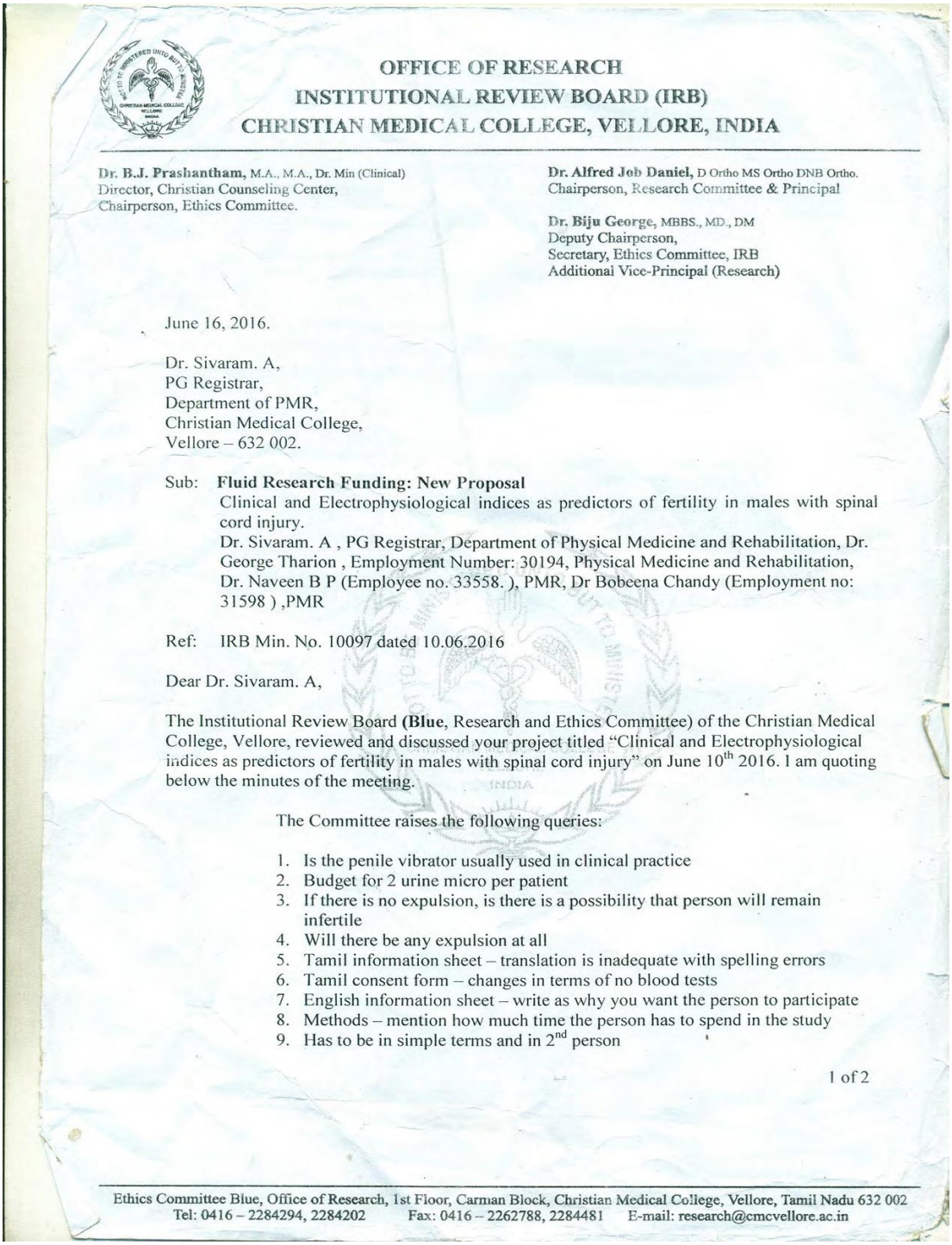

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

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

June 16, 2016.

Dr. Sivaram. A,
PG Registrar,
Department of PMR,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Funding: New Proposal**
Clinical and Electrophysiological indices as predictors of fertility in males with spinal cord injury.
Dr. Sivaram. A , PG Registrar, Department of Physical Medicine and Rehabilitation, Dr. George Tharion , Employment Number: 30194, Physical Medicine and Rehabilitation, Dr. Naveen B P (Employee no. 33558.), PMR, Dr Bobeena Chandy (Employment no: 31598) ,PMR

Ref: IRB Min. No. 10097 dated 10.06.2016

Dear Dr. Sivaram. A,

The Institutional Review Board **(Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Clinical and Electrophysiological indices as predictors of fertility in males with spinal cord injury" on June 10th 2016. I am quoting below the minutes of the meeting.

The Committee raises the following queries:

1. Is the penile vibrator usually used in clinical practice
2. Budget for 2 urine micro per patient
3. If there is no expulsion, is there is a possibility that person will remain infertile
4. Will there be any expulsion at all
5. Tamil information sheet – translation is inadequate with spelling errors
6. Tamil consent form – changes in terms of no blood tests
7. English information sheet – write as why you want the person to participate
8. Methods – mention how much time the person has to spend in the study
9. Has to be in simple terms and in 2nd person

1 of 2

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

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

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

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

Drs. Sivaram. A and George Tharion were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to **ACCEPT the proposal after receiving the suggested modifications and answers to the queries.**

Note:
1. Kindly HIGHLIGHT the modifications in the revised proposal.
2. Keep a covering letter and point out the answer to the queries.
3. Reply to the queries should be submitted within 3 months duration from the time of the thesis/ protocol presentation, if not the thesis/protocol have to be resubmitted to the IRB.
4. The checklist has to be sent along with the answers to queries.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Biju George, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

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

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

Cc: Dr. George Tharion, Department of PMR, CMC Vellore.

IRB Min. No. 10097 dated 10.06.2016

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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ANNEXURE-II

.

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

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

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

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

October 04, 2016

Dr. Sivaram. A,
Department of PMR,
Christian Medical College,
Vellore - 632 004.

Sub: **Fluid Research Funding: New Proposal**
Clinical and Electrophysiological indices as predictors of fertility in males with spinal cord injury.
Dr. Sivaram. A , PG Registrar, Department of Physical Medicine and Rehabilitation, Dr. George Tharion , Employment Number: 30194, Physical Medicine and Rehabilitation, Dr. Naveen B P (Employee no. 33558.), PMR, Dr Bobeena Chandy (Employment no: 31598) ,PMR.

Ref: IRB Min No: 10097 [OBSERVE] dated 10.06.2016

Dear Dr. Sivaram. A

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Clinical and Electrophysiological indices as predictors of fertility in males with spinal cord injury" on June 10th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Consent Form (English, Tamil, Hindi, Malayalam)
3. Patient Information Sheet (English, Tamil, Hindi, Malayalam)
4. Clinical Research Form
5. Cvs of Drs. Beena , Naveen, Tharion and Sivaram.
6. No. of documents 1 - 5

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

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Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
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Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on June 10th 2016 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist &Epidemiologist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Simon Pavamani	MBBS, MD	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

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

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Sathish Kumar	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. Rekha Pai	MSc, P.hd	Internal Basic Scientist, Int Basic Scientist, CMC, Vellore	External, Legal Expert
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS, MCh	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician

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: "Clinical and Electrophysiological indices as predictors of fertility in males with spinal cord injury" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:
A sum of 50,000/- INR (Rupees Fifty Thousand only) will be granted for 1 year.

Yours sincerely,

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

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

IRB Min No: 10097 [OBSERVE] dated 10.06.2016

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ANNEXURE III

PATIENT INFORMATION SHEET

Title of the study : Clinical and Electrophysiological indices as predictors of fertility in males with spinal cord injury.

Aim:The aim of the study is to assess the predictability of fertility using penile vibrator stimulation in persons with spinal cord injury using clinical responses and electrical nerve function studies.

Methods

Individuals like you who had spinal cord injury atleast 6 months prior to admission in Rehabilitation Institute with concerns of fertility will be given the option of joining the study. Approximately 72 patients will be participating in the study. Your history, clinical examination and nerve function tests as per proforma will be done by the primary investigator which will last for not more than 45 minutes. You will be given two trials of penile vibrator stimulation. Each trial of penile vibrator will be for a total duration of 10 minutes divided into two sessions of 5 minutes each and you will be given five minutes rest in between. Your urine will be collected before and after the vibrator stimulation for testing. In total, the time you need to spend for this study will be not more than 60 minutes. At the end of the study the data collected will be analysed.

Description of risks, discomforts or inconveniences:

You will not encounter any direct or indirect risks on participating in the study that will increase the present disability or cause death.

Unforeseeable risks: None

Anticipated benefits from the study:

You can know about your chances of fertility following participation in the study.

Clinicians involved will be able to know whether fertility with penile vibrator can be predicted using clinical tests.

Compensation for participation:

Since there is no direct or indirect risk for you causing increase in disability or death, there is no such provision for compensation.

What happens if you choose to withdraw from study participation?

Your participation in the study will be voluntary. There will be no change in treatment or future management even if you withdraws from the study. Information gained from you will not be used for any publication or study purpose.

ANNEXURE IV

INFORMED CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Fertility in males with spinal cord injury patients can be predicted by clinical and electrophysiological methods.

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 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. [ ]

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

Date: _____/_____/_____

Signatory's Name: _____ Signature:

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: _____

ANNEXURE-V

CLINICAL RESEARCH FORM

CLINICAL AND ELECTROPHYSIOLOGICAL INDICES AS PREDICTORS OF FERTILITY IN MALES WITH SPINAL CORD INJURY

Date of study

Unique study ID number

Name Age

Hospital number

Address

District State

Contact landline number

Contact mobile number

Level of Injury

Vertebral level

Neurological level

ASIA scale grade

Mode of injury

Time since injury

Age of injury

Married/Unmarried

If married, number of children

Sexual History before injury

Erection	Ejaculation

Sexual history after the injury

Erection	Ejaculation

Was semen in urine noticed by the patient?

Any history of Epididimo orchitis (Yes/No)

Any Prolonged drug usage (Yes/No)

Bladder managed by (ICC/ CBD / Selfvoid)

Occupation (Manual/Professional/Student/Unemployed)

Annual income (upto 40000/40000-2.5lakh/above 2.5lakh)

Any addictions

Any history of heart disease/ Diabetes/ hypothyroidism/ hypertension

PHYSICAL EXAMINATION

Height

Weight

BMI (Underweight/Normal/Overweight/Obese)

Pulse rate

BP

Peripheral Pulses all felt (Yes/No)

Thyroid enlargement present (Yes/No)

Gynecomastia present (Yes/ No)

Features of Hirsuitism present (Yes/No)

NEUROLOGICAL EXAMINATION

Higher mental functions

Cranial Nerve Function normal (Yes/No)

Motor System

Muscle wasting present (Yes / No)

Tone by MAS

Right upper limb	
Left upper limb	
Right lower limb	

Left lower limb	

Power

Elbow Flexors	C5		
Wrist Dorsiflexors	C6		
Elbow Extensors	C7		
Long finger flexors	C8		
Small finger Adductor	T1		
Hip Flexors	L2		
Knee Extensors	L3		
Ankle Dorsiflexors	L4		
Big Toe Extensors	L5		
Ankle Plantar Flexors	S1		

Voluntary anal contraction present (Yes/No)

Sensory Testing

Sensory level	Fine touch	Pin prick
T6		
T7		
T8		
T9		
T10		
T11		
T12		
L1		
L2		
L3		
L4		
L5		
S1		
S2		

S3		

Perianal Sensation present (Yes / No}

Deep Anal Sensation present (Yes /No)

Reflexes

Knee jerk		
Ankle jerk		

Abdominal Reflexes

Plantar Reflex (Flexor/Extensor)

Any Knee flexor response

Any hip flexor response

Cremasteric Reflex

Bulbocavernous reflex

Rectal muscle tone

Pressure sore present (Yes/No)

if present position & MUAP grading

Any contractures

Genital Examination

External genitalia, scrotum and testis normal (Yes/ No)

Any local inflammation (Yes / No)

Ulcerations present (Yes / No)

Tenderness over scrotum present (Yes / No)

Electrophysiological Assessment

Soleus H reflex

H reflex Onset Latency		

F wave posterior tibial nerve

Mean F wave latency		

Penile vibrator stimulation

Trial 1 Ejaculation present (Yes/ No) Trial 2 Ejaculation present (Yes/ No) Somatic responses present (Yes/No)

Urine Microscopy

Semen present in urine samples (Yes/No)

ANNEXURE-VI

DATASHEET

DATE	IDNO	AGE	MCI	TIMSIN	AGS	NEUR	MARR	VER	CHI	LIB	EF	B4E	J..	AFT	AFT	SEN	DRU	TYPE	BLAD	WORK	ADD	PAS	SUR	BMI	PE	TH	GYN	HIR	WA	TON	TON	TON	TON	TON	TON	EPO	PO	PO	PO	POM	POM	EI
01/09/2016	1001	41	2	156	27	2	2	2	0	1	1	2	2	1	2	8	4	1	7	8	7	26.2	1	2	2	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
02/09/2016	1002	24	2	11	23	1	2	1	0	1	1	1	1	1	2	8	4	4	9	8	7	19.5	1	2	2	2	3	3	3	3	3	3	3	0	0	0	0	0	0	0
04/09/2016	1003	24	1	50	20	2	2	2	0	1	1	1	2	2	2	7	4	4	6	8	7	17.6	1	2	2	2	1	4	3	4	4	4	3	0	0	0	0	0	0	0
01/10/2016	1007	31	1	6	30	2	1	2	1	1	1	1	2	1	2	8	4	1	6	8	7	21.2	1	2	2	2	3	1	1	2	3	1	1	0	0	0	0	0	0	0
08/10/2016	1008	30	3	76	24	2	2	2	0	1	1	2	2	1	2	8	4	1	2	8	7	29	1	2	2	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
16/10/2016	1009	36	2	31	33	2	1	2	2	1	1	2	2	1	2	8	4	1	7	8	6	18.4	1	2	2	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
26/10/2016	1010	46	3	226	26	2	2	2	0	1	1	2	2	1	1	2	4	1	6	8	7	23	1	2	2	2	1	2	1	2	1	3	2	0	0	0	0	0	0	0
26/01/2017	1011	30	1	32	27	1	1	1	2	1	1	1	2	1	2	8	4	1	6	8	7	19.4	1	2	2	2	3	4	4	4	4	4	4	0	0	0	0	0	0	0
02/02/2017	1012	38	3	12	37	2	1	2	0	1	1	1	2	1	2	8	4	1	1	8	7	24.8	1	2	2	2	3	1	1	1	1	1	1	0	0	0	0	0	0	0
05/09/2016	1004	27	3	51	23	1	2	2	0	1	1	1	1	1	2	8	4	1	8	8	7	18.59	1	2	1	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
07/09/2016	1005	41	1	15	40	2	1	2	2	1	1	1	2	2	2	8	4	1	6	8	7	25.78	1	2	2	2	3	6	6	6	6	6	6	0	0	0	0	0	0	0
24/09/2016	1006	29	1	42	25	2	2	2	0	1	1	1	2	1	1	2	3	1	7	8	6	23.01	1	2	2	2	1	5	4	5	2	3	2	0	0	0	0	0	0	0
13/02/2017	1013	35	3	84	28	1	1	1	0	1	1	1	2	1	2	8	2	2	6	1	7	26.9	1	2	1	2	1	1	1	1	1	1	1	0	0	0	0	0	0	0
05/03/2017	1014	35	1	6	34	2	1	2	2	1	1	1	2	1	2	8	4	1	8	8	7	27.5	1	2	2	2	3	6	6	6	6	6	6	1	0	0	0	0	0	0
26/02/2017	1015	38	3	7	37	2	1	2	2	1	1	1	2	2	1	7	4	6	6	1	7	22.1	1	2	2	2	3	6	6	6	6	6	6	0	0	0	0	0	0	0
26/02/2017	1016	24	1	17	22	2	1	2	0	1	1	1	2	2	2	2	4	1	6	8	7	21.7	1	2	2	2	3	3	3	4	4	2	2	0	0	0	0	0	0	0
02/03/2017	1017	38	3	10	37	2	1	3	3	1	1	1	2	2	2	8	3	1	8	8	7	19.5	1	2	2	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
28/03/2017	1018	37	2	10	36	2	1	2	0	1	1	1	1	1	2	8	4	1	8	8	7	18.4	1	2	2	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
04/04/2017	1019	47	1	44	44	2	1	3	2	1	1	1	1	1	2	7	4	1	6	8	7	22.5	1	2	2	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
17/04/2017	1020	30	1	9	29	2	1	2	0	1	1	1	2	2	2	8	3	3	6	8	7	24.2	1	2	2	2	3	2	2	2	2	2	2	0	0	0	0	0	0	0
17/05/2017	1021	24	6	72	18	2	1	3	0	1	1	1	1	2	2	8	4	1	6	8	7	19.5	1	2	2	2	1	6	6	6	6	6	6	0	0	0	0	0	0	0
21/07/2017	1022	31	1	36	28	2	2	2	0	1	1	1	2	2	2	8	4	1	1	8	7	16.01	1	2	2	2	1	6	6	6	6	6	6	3	3	2	2	0		
08/08/2017	1023	28	3	36	25	2	1	2	1	1	1	1	1	1	1	2	4	1	8	8	1	22.8	1	2	2	2	3	4	4	4	4	3	3	0	0	0	0	0	0	0

FT	FTL	FT	F'	F'	FT	F'	F	F'	F'	FT	F1	F	F'	FT	F1	FTI	FTL	PP	PP	PP	PF	PF	PF	PF	PP	PP	PF	PF	P	PI	PF	PF	P	PF	PA	DA	KJ	K	A	A	R	L	R	L	P	PL	KF	L	R	LH	RC	LC	B	RE	GE	GE	S	SC	ONSET	ONETL	PT	LF	RP	LP	TR	TR	EJ	SC	SC	UR
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