CHAPTER 5

METHODOLOGY

5.0. METHODS

5.1 PARTICIPANTS

5.1.1 Sample size: The sample size was calculated using G-power software by fixing the alpha at 0.05 powered at 0.8 and the effect size of 0.55 based on the mean and standard deviation of the Spinal Cord Independence Measure (SCIM) from the previous study (Sander Hitzig et al., 2013). The optimal sample size was 62 participants in each group.

5.1.2 Selection and source of participants: A total of 157 SCI patients who were admitted to the Swami Vivekananda National Institute of Rehabilitation, Training, and Research (SVNIRTAR), Odisha, India, were screened using ASIA scale during the period between April 2018 to October 2018.

5.1.3 Inclusion criteria: Inclusion criteria included:

- Patients admitted to Swami Vivekananda National Institute Rehabilitation, Training, and Research (SVNIRTAR), Odisha.
- Incomplete SCI patient (American spinal injury Association impairment scale (AIS) C and (AIS) D with injury to the spinal cord from level anywhere between T1 to L5.
- Patients of both genders and with the age range of 18-60 years.
- Patients who are willing to participate in the study.
- Have sustained a traumatic spinal cord injury for a minimum of 6 months prior to consent and have completed their primary rehabilitation.

5.1.4 Exclusion criteria: Patients were excluded from the study if they:

- Have any contraindications to FES such as a cardiac pacemaker, epilepsy, lower limb fracture or pregnancy.
- Are likely to experience clinically significant autonomic dysreflexia and/or orthostatic hypotension in response to electrical stimulation or prolonged upright postures.
- Have chronic systemic diseases, e.g., hepatitis C or HIV-AIDS
- Have an existing stage 3 or 4 pressure ulcer according to the National Pressure Ulcer Advisory Panel classification.
- Have had recent major trauma or surgery within the last 6 months
- Have degenerative myelopathy, neoplasm, or congenital spinal cord anomalies.
- Have concomitant medical problems that might have influenced everyday function, such as malignancy, brain injury or mental diseases were excluded.

5.1.5 Ethical consideration: The study was approved by the Institutional Ethics Committee of University (RES/IEC-SVYASA/93/2016), and the research protocol was registered in the Clinical Trial Registry of India (CTRI/2018/07/014779). Signed informed consent was obtained from the head of the institution and each participant, upon explaining the study details.

5.1.6 Screening tool:

StandardizedneurologicalexaminationprotocoloftheAmericanSpinalInjuryAssociation(ASIA). International Standards for Neurological Classification of Spinal Cord Injury (ASIA Impairment Scale) classifies motor and sensory impairment as follows:

- ***ASIA A*** – No motor or sensory function is preserved below the level of injury (and in the sacral segments S4 – S5).
- ***ASIA B*** – Sensory but not motor function is preserved below the neurological level (includes the sacral segments S4 – S5).
- ***ASIA C*** – Motor function is preserved below the neurological level, but too little to represent a practically usable function (more than half of key muscles below the neurological level have a muscle grade less than 3).
- ***ASIA D*** – Motor function is preserved below the neurological level, to an extent that provides practically usable function (at least half of key muscles below the neurological level have a muscle grade of 3 or more on a scale from 0 to 5).
- ***ASIA E*** – Motor and sensory functions are normal.

ASIA A implies a complete injury, **ASIA B – D** describe incomplete injuries.

5.2 DESIGN OF THE STUDY

This was a single-blind pre-post randomized controlled trial where all participants were randomly divided into two groups: (i) add-on yoga and physiotherapy group (IYP), and (ii) physiotherapy group (PT). Prior to randomization, each participant was assessed at the baseline.

5.2.1 Randomization:

A total of 124 participants were assigned in two groups, 62 in each, using computer-based random number generator. The 124 participants were randomized in two groups as follows:

(i) Each participant was given a serial number from 1 to 124, which did not depend on their order of enrollment, their surname or any other factor.

(ii) A specific computer program (http://www.random.org/sequences) was used to generate 124 random numbers. The 124 random numbers were written beside the serial numbers. Hence each participant was assigned a random number.

(iii) The random numbers were written on identical envelopes alternately into two boxes, one labeled A, and the other B. 124 envelopes were prepared and each participant was asked to pick an envelope.

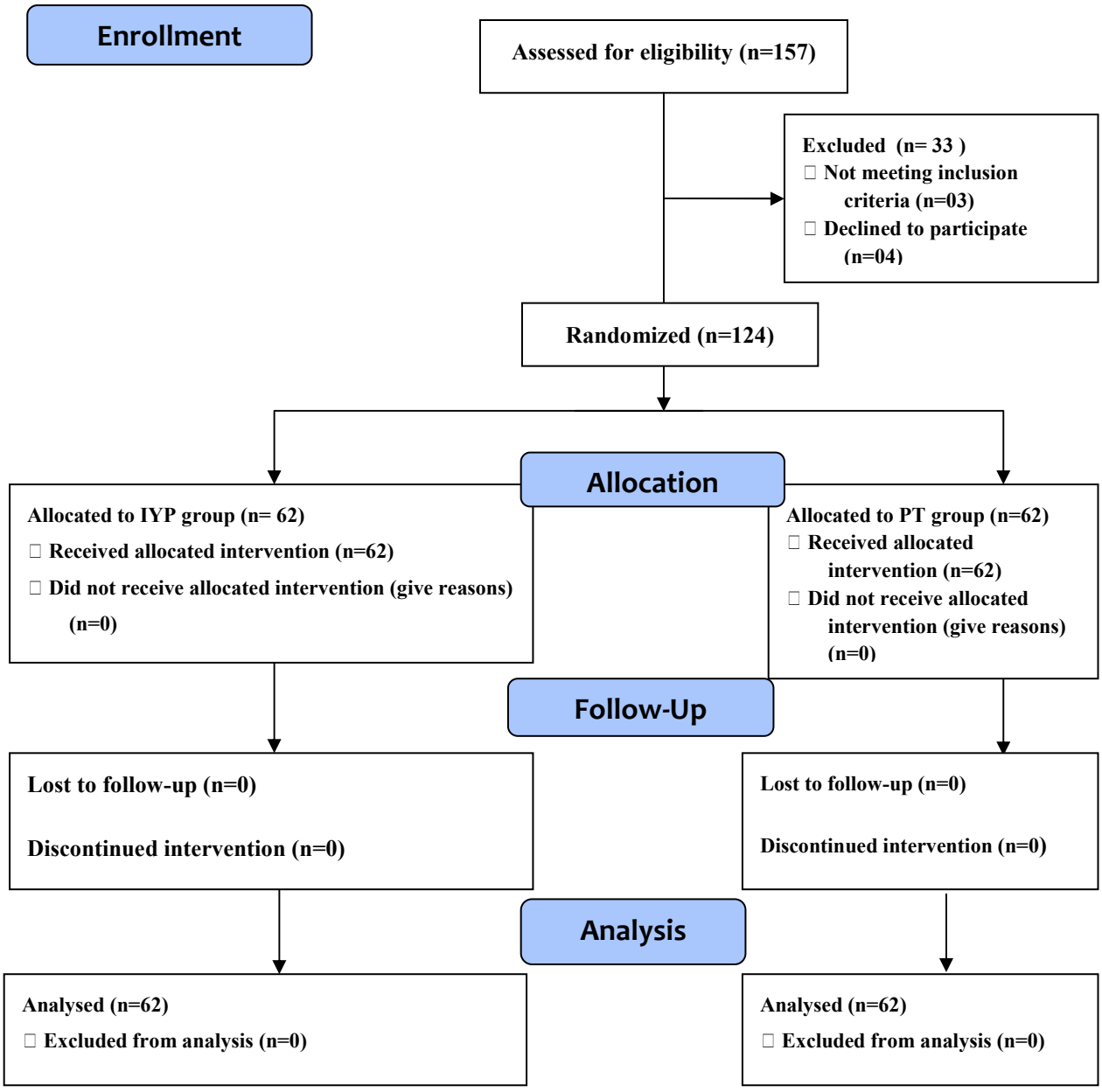
(iv) A coin was tossed and it was pre-determined that if tossing results in 'HEAD', then person in A were allocated to IYP group and persons in the B group were allocated to PT group. Through this method of randomization, both groups were allocated 62 participants each. Hence the study design has an allocation ratio of 1:1.

(v) Depending on the number in the envelope, participants were considered either in IYP group or in PT group {known as sequentially numbered opaque sealed envelopes (SNOSE) randomization technique}.

5.2.2 Blinding:

The statistician (who did the randomization and analyzed the data)was blinded to the source of the data and regarding members of the intervention groups.

Figure 8: CONSORT Flow Diagram



5.3 VARIABLES STUDIED

Primary outcomes

American Spinal Injury Association (ASIA) Impairment Scale

The ASIA Impairment Scale is an improvisation of the earlier Frankel scale. The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) was developed by the American Spinal Injury Association (ASIA) as a universal classification tool for spinal cord injury (SCI), depending upon the motor and sensory impairment that results from an SCI. The additional anorectal examination is essential for determining the completeness of the injury and evaluating for the presence of spinal shock (Kirshblum et al., 2011).Generally, the inter-rater reliability of this scale is high: motor = 0.97, Light Touch (LT) = 0.96, Pin Prick(PP) = 0.88. Repeatability values are small in patients with complete SCI (motor < 2 points, sensory < 7 points) but large for patients with incomplete SCI. Intra-rater reliability values were ≥ 0.98 for patients with complete SCI. The summed scores for motor, LT, and PP in subjects with complete SCI have high inter-rater reliability and small repeatability values. These measures are appropriately reliable for use in clinical trials involving serial neurological examinations with multiple examiners(Marino, Jones, Kirshblum, Tal, & Dasgupta, 2008).

Walking index for SCI II (WISCIII)

Walking Index for Spinal Cord Injury acronymed as WISCI II assesses the amount of physical assistance needed, as well as devices required, for walking following paralysis that results from Spinal Cord Injury (SCI). Designed to be a more precise measure of improvement in walking ability specific to SCI. It ranks orders the ability of a person to walk 10m after a spinal cord injury from most to least severe impairment. WISCI II has been broadly accepted due to its high validity across multiple dimensions. The

hierarchical ranking agreed on by the 24 experts in SCI walking function established content and face validity. A previous prospective study of 170 participants in four countries confirmed that sequence through the levels followed a monotonic pattern in more than 80% of subjects, and the correlation of walking capacity (WISCI II) with impairment lower extremity motor score (LEMS) was 0.91 (P<0.001) at final evaluation, supporting content and construct validity. Other studies have shown a correlation between the WISCI II and mobility measures such as the 10MWT, Timed up and Go test,6-min walk test (6MWT), Berg Balance Scale, SCIM, and Spinal Cord Injury-Functional Ambulation Profile (Ditunno et al., 2013).The intra-rater reliability for maximal level WISCI II was 1.00, and inter-rater reliability was 0.98 (Ditunno et al., 2000).

Modified Modified Ashworth Scale to measure spasticity (MMAS)

The Modified Modified Ashworth Scale (MMAS) is a clinical instrument for measuring spasticity. The Ashworth Scale was originally developed in 1964, and modified by Bohannon and Smith in 1987.The Bohannon-Smith Modified Ashworth Scale (MAS) has been recently modified by Ansari *et al* 2006 as the Modified Modified Ashworth Scale. The MMAS is an ordinal level measure of spasticity, which grades the intensity of spasticity from 0 to 4.The MMAS score with the clear definitions and hierarchical relationship of the grades of 1 and 2 have an ordinal relationship by omitting the grade "1+" and redefining grade "2, " that would be more valid for grading the lower grades of spasticity. The results of several studies have demonstrated that the MMAS is a reliable measure for assessing spasticity in either upper or lower limbs of patients with spasticity. Previous research shows high inter-rater or intra-rater reliability of the MMAS (Bohannon & Smith, 1987). Following is the description of the scale:

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
2	Marked increase in muscle tone, manifested by a catch in the middle range and resistance throughout the remainder of the range of motion but affected part (s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Bio-marker: c-Reactive Protein (CRP)

C-reactive protein (CRP) is a stable plasma biomarker for inflammation in the body. It is a circulating pentraxin that has a major role in the human innate immune response and produced majorly in the liver as part of the acute phase reactant, which means that its level will rise in response to inflammation. It is also produced in smooth muscle cells within diseased atherosclerotic arteries and has been associated with many aspects of atherogenesis and plaque vulnerability, including the production of adhesion molecules, induction of nitric oxide, altered complement function, and inhibition of intrinsic fibrinolysis. Individuals with chronic spinal cord injury (SCI) have clinical characteristics that promote systemic inflammation and these clinical characteristics common in chronic SCI are associated with plasma CRP (Goldstein et al., 2017).

It is usually measured in milligrams of CRP per liter of blood (mg/L). There is presently no set standard for CRP blood levels, and guidelines vary.However, as a general rule, the following applies to CRP:

- Levels between 3 mg/L and 10 mg/L are mildly elevated and usually result from chronic conditions such as diabetes, hypertension, or lifestyle factors, including tobacco smoking and being sedentary.
- Levels between 10 mg/L and 100 mg/L are moderately elevated and are usually due to more significant inflammation from an infectious or non-infectious cause.
- Levels above 100 mg/L are severely elevated and almost always a sign of severe bacterial infection.

The hs-CRP test results indicate a person's risk of developing cardiovascular disease (CAD) accordingly:

- Low risk is lesser than 1 mg/L.
- Moderate risk is between 1 mg/L and 3 mg/L.
- High risk is greater than 3 mg/L.

Erythrocyte sedimentation rate (ESR)

The Erythrocyte Sedimentation Rate (ESR) is a simple and inexpensive laboratory test for assessing the inflammatory or acute response. It is a type of blood test that measures how quickly erythrocytes (red blood cells) settle at the bottom of a test tube that contains a blood sample. Normally, red blood cells settle relatively slowly.

The International Committee for Standardization in Hematology (ICSH) recommends the use of the Westergren method. While the role of acute-phase reactants and cytokines in inflammatory responses is well-established, ESR measurement remains the method of choice in evaluating different clinical conditions. The ESR has also been found to be of clinical significance in the follow-up and prognosis of non-inflammatory conditions such

as prostate cancer, coronary artery disease, and stroke. Therefore, the ESR is important in the diagnosis of inflammatory conditions and in the prognosis of non-inflammatory conditions.

Measurement of the distance in millimeters that erythrocytes fall from the top of a vertical tube during one hour for the evaluation and management of inflammatory states; serves as a marker of red cell aggregation. ESR test results are measured in millimeters per hour (mm/hr).

It is used to detect illnesses associated with acute and chronic infection, advanced neoplasm, and tissue necrosis or infarction.

Normal ESR test results:

- Women under age 50 should have an ESR between 0 and 20 mm/hr.
- Men under age 50 should have an ESR between 0 and 15 mm/hr.
- Women over age 50 should have an ESR between 0 and 30 mm/hr.
- Men over age 50 should have an ESR between 0 and 20 mm/hr.
- Children should have an ESR between 0 and 10 mm/hr.

A faster-than-normal rate may indicate inflammation in the body. It can be a reaction to an infection or injury. ESR can be a marker of altered immune response seen in people with SCI (Edsberg, Jennifer, Rajna, et al., 2015).

Spinal Cord Independence Measure (SCIM)

Functional recovery may or may not follow/translate into neurologic recovery. SCIM III is a sensitive outcome measure designed to assess functional status relevant to SCI. It can be used as a scale in traumatic and non-traumatic, acute and chronic SCI. There are a total of 19 items on the SCIM III, which are divided into 3 subscales (self-care, respiration and

sphincter management, and mobility) (Catz, Itzkovich, Agranov, Ring, & Tamir, 1997).In a reliability and validity multi-center cohort study for SCIM III, a total agreement between raters was above 80% in most SCIM III tasks, and all kappa coefficients were statistically significant ($P < 0.001$). The coefficients of Pearson correlation between the paired raters were above 0.9, and intra-class correlation coefficients were above 0.94. Cronbach's α was above 0.7. The coefficient of Pearson correlation between FIM and SCIM III was 0.790 ($P < 0.01$). SCIM III was more responsive to changes than FIM in the subscales of Respiration and sphincter management and Mobility indoors and outdoors. Thus, SCIM III is an efficient measure for functional assessment of SCL patients and can be safely used for clinical and research trials, including international multi-center studies(Itzkovich et al., 2007).

Multidimensional Pain Inventory (Spinal Cord Injury Version) – MPI-SCI

A spinal cord injury version of the MPI that assesses the severity and impact of chronic pain, emotional and physical adaptation to persistent pain, and social support. With the exception of the support and life control sub-scales, all others showed adequate test-retest reliability. Each item is scored on a 7-point scale (Turk et al., 1983).

The internal consistency of the MPI-SCI subscales ranged from fair (.60) for affective distress to substantial (.94) for pain interference with activities. The subscales of the MPI-SCI (i.e., life interference [r=.81], affective distress [r=.71], solicitous responses [r=.86], distracting responses [r=.85], general activity [r=.69], pain interference with activities [r=.78], pain severity [r=.69], negative responses [r=.69]) showed adequate stability. In contrast, the stability of the support (r=.59) and the life control subscales (r=.31) was unacceptably low. All MPI-SCI subscales with the exception of the perceived responses by significant other subscales showed good convergent, discriminant, and concurrent validity. Thus, the MPI-SCI is a sensible measure for evaluating chronic pain

impact after SCI (Widerström-Noga, Cruz-Almeida, Martinez-Arizala, & Turk, 2006).

Medical-Based Emotional Distress Scale (MEDS)

*The Medical-Based Emotional Distress Scale (MEDS)*assesses depression. This instrument is developed specifically to evaluate the kind and severity of emotional distress following a physical illness, injury, or disability. In order to prevent confusion between physical symptoms derived from SCL and physical symptoms derived from a potential depression, the MEDS focuses on cognitive and emotional factors of depression and avoids the use of somatic symptoms. MEDS was originally designed to be administered as a structured interview, butin the present studyis used as a self-report measure. The MEDS is a 60-item clinician-administered questionnaire to assess emotional reactions to severe physical illness or disability and measures distress along seven subscales: Dysphoria, Irritability, Anhedonia, Social Withdrawal, Ruminations over Past Events, Cognitive Perspective in the Present, and Expectations for the Future (Overholser, James, Schubert, Daniel, Foliart, Roland, Frost, 1993).

A total MEDS score correlates significantly with other distress and depression measures, that is, the Symptom Checklist-90-Revised (r=0.77), the Zung Self-Rating Depression Scale (r=0.71), and the Rosenberg SE Scale (r=−0.75). The MEDS includes seven subscales: dysphoria (eight items), irritability (nine items), anhedonia (11 items), social withdrawal (nine items), rumination over past events (six items), cognitive perspective in the present (eight items), and expectations for the future (nine items)(Nielsen, 2003).

Two different 5-point scales are used. One quantifies the frequency of different emotional reactions ranging from ‘never’ (0) to ‘always present’ (4), and one rate the intensity of emotions that occurred ranging from ‘not present’ (0) to ‘very much present’ (4). The internal consistency for the total MEDS score is 0.92 and all subscales

show moderately high internal consistency.

Secondary outcomes

Quality of Life Index Spinal Cord Injury - Version III

The *Ferrans and Powers Quality of Life (QLI)* emerged its specific version for spinal cord injury, known as *QLI Spinal Cord Injury - Version III* and is an index of 74 items divided into two parts: satisfaction and importance. It was developed by Carol Estwing Ferrans and Powers Marjorie in 1984 (Estwing Ferrans & Powers, 1998) to measure quality of life specifically in people with spinal cord injury. It can be administered by interview or by self-report and contains 37 items and each item is rated on a scale of 1 (least satisfied/important) to 6 (most satisfied/important). No values were reported for the reliability of the QLI for the SCI population. Correlation of the QLI is highfor the Reintegration to Normal Living Scale (Pearson's r=-0.654) and the Rosenberg Self-Esteem Scale (Pearson's r=0.609)(May & Warren, 2001).

Anthropometry: Body Mass Index (BMI)

The body mass index (BMI), or Quetelet index, is a measure of relative weight based on an individual's mass and height (Nuttall, 2015). It is defined as the individual's body mass divided by the square of their height and is universally being given in units of kg/m^2.

Obesity or excess body fat is measured by different means and one of the most commonly used methods is to compute an index of body weight as a function of height and to compare this calculation to population standards, known as the body mass index (BMI). BMI estimates total body mass rather than fat mass, but it correlates highly with the amount of body fat.

According to WHO, adults are classified according to BMI as follows:

Classification	BMI	Risk of co-morbidities
Underweight	< 18.50	Low
Normal Range	18.50 – 24.99	Average
Overweight/Pre-obese	25.00 – 29.99	Increased
Obese Class I	30.00 – 34.99	Moderate
Obese Class II	35.00 – 39.99	Severe
Obese Class III	≥ 40.00	Very severe

For measuring the height, the recumbent length of the study participants was measured by making them lie in supine on a raised mat table. Height was then recorded to the nearest 1/16 of an inch (Froehlich-Grobe, Nary, Van Sciver, Lee, & Little, 2011). Total weight was measured using a Wheelchair (WC) platform scale and the participant's weight was recorded with his/her WC. The participant then transferred out of his/her WC, and the WC was weighed alone. Bodyweight was calculated by subtracting WC weight from the total weight. Body mass index has good general correlation with BF %, but it fails to

discriminate between body fat % (BF %) and lean mass. In addition, the sensitivity of BMI ≥ 30 kg/m^2 to diagnose obesity is relatively low, missing more than half of people with BF %defined obesity, while the specificity and positive predictive value are good. In addition, for a given BMI value there is significant inter-subject variability in BF %(May & Warren, 2002).

5.4 INTERVENTIONS

Participants in the IYP group received 75 minutes (6 days/week)ofan integrated yoga intervention for one month. Data collections were done on Day 1 and Day 30. Participants of both the intervention (IYP) and control (PT) groups recruited from the same rehabilitation center had uniform diet, sleep-day cycle, and social environment and were exposed to the same rehabilitation protocol as mentioned in column "Passive Therapy" in table 7 and table 8. As intervention, the IYP group received yoga therapy special technique for spinal cord injury and also practiced mind sound resonance technique. On the other hand, the matched control group (PT) practiced active range of motion exercises (AROM) and listened to soothing music. All practices included in the yoga practice protocol were safe, feasible and have been adapted for the intervention with consent from authors of the previous study (Patil, Nagaratna, Garner,Raghuram, & Crisan, 2012).An attendance register was maintained to monitor the attendance of the participants. A Cut –off of 70% attendance was kept to consider for analysis.

YOGA THERAPY FOR IYP GROUP: The specific module of yoga therapy for SCI management was developed by using the concepts from traditional yoga scriptures (*Patanjali Yoga Sutras, Upanishads and Yoga Vashishtha*) that highlight a holistic approach to health management at physical, mental, emotional and intellectual levels. The practices consisted of yogic postures (*asanas*), breathing practices (*pranayama*), cleansing techniques (*kriya*), relaxation techniques, meditation and yogic counseling, chosen specifically for SCI. SCI special techniques progressed from safe yogic movements to yoga postures that provide traction like effect and channelize the vital energy flow all through the spine, as represented in Table 6.

Table 5: The details of yoga therapy practices.

S. N.	Type of Practice	Practice Name (Sanskrit and English)	Duration of Practice
1	**Loosening practices/ *Sukshma Vyayama* of Upper limb**	Finger movements	5 Min. (5 rounds each movement)
		Wrist movements	
		Elbow movements	
		Shoulder movements	
2	**Loosening practices/ *Sukshma Vyayama* of Lower limb (With or without support)**	Toes movements	5 Min (5 rounds each movement)
		Ankle movements	
		Knee movements	
		Hip movements	
3	***Asanas* (with support or props)**	*Padahastasana* (Hand Under Foot Pose)	2 Min (2 repetitions)
		Ardhachakrasana (Half-moon pose)	2 Min (2 repetitions)
		Ardhakati Chakrasana (Half waist rotation pose)	2 Min (2 repetitions)
		Vakrasana (Half Spinal Twist Pose)	2 Min (2 repetitions)
4	***Kriya***	*Kapalbhati* (High frequency yoga breathing)	2 Min (15 rounds)
5	***Pranayama***	*Vibhagiya Pranayama* (Sectional Breathing)	4 Min (6 rounds)
		Nadishuddhi (Alternate nostril breathing)	2 Min (6 rounds)
		Bhramari (Humming Sound Breathing)	2 Min (9 rounds)
		Bhastrika (Rapid ventilation breathing practice)	2 Min (6 rounds)
6	**Relaxation Practice**	Deep Relaxation Technique	10 Min
		Mind Sound Resonance Technique	30 Min

FOR BOTH GROUPS: The Physiotherapy intervention was common and consisted of (i) proprioceptive neuromuscular facilitation (PNF), (ii) slow and sustained stretching, (iii) prolong icing, (iv) strengthening of anti-gravity muscles, (v) functional electrical stimulation, and (vi) gait training. Physiotherapy sessions for both the groups lasted for 75 min/day and 06 days/week for one month.

Table 6: Time-table for Physiotherapy group.

THERAPHY	INTERVENTION	TIME PERIOD
Active Therapy	1. Active range formation exercise (AROM) 2. Listening to soothing music	45 minutes 30 minutes
Passive Therapy	3. Proprioceptive Neuro-muscular Facilitation 4. Slow and Sustained stretching 5. Prolong icing 6. Strengthening of Anti-spastic muscles 7. Functional Electrical Stimulation 8. Gait training	20 minutes 45 minutes 30–45 min 45-60 min 30 min 15 min
Counseling	Psychological Counseling	40 min. twice/week

Table 7: Time-table for Yoga and Physiotherapy group.

THERAPHY	INTERVENTION	TIME PERIOD
Active Therapy	1. Yoga Special Technique for Spinal Cord Injury 2. Mind Sound Resonance Technique (MSRT)	45 minutes 30 minutes
Passive Therapy	3. Proprioceptive Neuro-muscular Facilitation 4. Slow and Sustained stretching 5. Prolong icing 6. Strengthening of Anti-spastic muscles 7. Functional Electrical Stimulation 8. Gait training	20 minutes 45 minutes 30–45 min 45-60 min 30 min 15 min
Counseling	Yogic Counseling	40 min. twice/week

5.5 DATA EXTRACTION

Data was collected on day1 and at the end of one month. The investigators were available to answer the questions and provide unbiased guidance during the assessment. Data entry was completed by the research student, under the guidance of the study statistician. All forms were thoroughly screened for completeness of response.

5.6 DATA ANALYSIS

Data were analyzed using the R-Studio. Shapiro-Francia test was used to check the normality of data distribution. Gender and other categorical variables were analyzed using the Chi-square test. *Mc-Nemar* test was used to analyze within the group differences in Categorical Variables. The independent sample‘t’ test was used for between-groups analysis and paired sample‘t’ test was used for within-group change from pre to post at Day1 and Day30. The Pearson correlation was done between age and outcome measured variables. The level of significance considered for the present study was $p<0.05$.