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Functional Electrical Stimulation for Physiotherapy Management of Neurological Conditions: An Evidence Based Study

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ABSTRACT

Functional Electrical Stimulation is the electrical stimulation of motor neurons such that muscle groups are stimulated to contract & create a moment about a joint. In recent years, FES is relatively used as a new therapeutic tool in rehabilitation program of different neurological conditions. Although FES has been used for long time for treating foot drop, there are many studies which support the beneficiary effect to improve upper and lower extremity's function, spasticity, subluxation, respiration, balance, gait training, activities of daily living, quality of life. Multiple databases were searched for relevant articles. The purpose of this study is to evaluate the effectiveness of FES in different neurological condition and to collect the existing literature dealing with FES in a single article to analyze the result & to finally reach the overall conclusion.

Keywords: FES, Stroke, Spinal Cord Injury, Multiple Sclerosis, Parkinsonism.

INTRODUCTION

Functional Electrical Stimulation is the electrical stimulation of motor neurons such that muscle groups are stimulated to contract and create a moment about a joint.[(1)] The neurons receive a series of short electrical pulses that are delivered using electrodes. These electrodes can be transcutaneous, percutaneous, epimyseal or cuff.[(2)] Application of FES can be independent or dependent. FES independent application is the use of FES for finite time period to minimize impairments and to encourage motor relearning in context of function. FES dependent application is the use of FES that enables the patient to perform functional activities that wouldn't otherwise be possible. Functional Electrical Stimulation was initially referred to as Functional Electrotherapy by Liberson and it was not until 1967 that the term Functional Electrical Stimulation was established by Moe & Post. The first commercially available FES device treated Foot Drop in hemiplegic patients by stimulating the peroneal nerve during gait.[(3)]

In recent years, FES is relatively used as a new therapeutic tool in rehabilitation program of different neurological conditions like Stroke, Spinal cord injury, Multiple Sclerosis, Parkinson's disease, Cerebral Palsy, Hereditary Spastic Paraparesis, etc. Although FES has been used for long time for treating foot drop, there are many studies which support the beneficiary effect to improve upper and lower extremity's function, spasticity, subluxation, respiration, balance, gait training, activities of daily living, quality of life.

FES application alone or in conjunction with other regular rehabilitation programs for different neurological condition can have a better rehabilitation outcome. The main purpose of this study is to have evidence in order to evaluate the effectiveness of FES in neurorehabilitation.

Another purpose of the present study is to collect the existing literature dealing with Functional Electrical Stimulation in a single article to analyze the results and finally to reach the overall conclusion.

METHODOLOGY

In order to collect evidences for the effectiveness of FES in different neurological conditions like Stroke, Spinal Cord Injury, Multiple Sclerosis, Parkinsonism, Cerebral Palsy, Hereditary Spastic Paraparesis, Foot Drop, etc. articles were searched and gathered.

The articles were searched in search engines like Google Scholar, PubMed, Cochrane library, Research gate, Elsevier & Medline. Keywords like FES, Stroke, SCI, Parkinsonism, Cerebral palsy, Paraparesis were used. The reference articles were taken from BioMed Research International, Topic Stroke Rehabilitation, Neurorehabilitation, Physiotherapy Canada, Journal of Physical Therapy, Journal of Spinal Cord Medicine, International Journal of Multiple Sclerosis care, Multiple Sclerosis related Discord, Journal Rehabilitation & Assistive Technologies Engineering, Developmental Medicine & Child Neurology, Pediatric Physical Therapy, Journal of Rehabilitation Medicine. These articles were taken with references to explain FES and its effect on different neurological conditions. Guidelines for evidence based clinical practice were adapted from Oxford Centre for Evidence Based Medicine (The Oxford 2011 Level of Evidence).

❖ **Inclusion criteria**

- Articles published from 2010 to 2020.
- Article should be published in English language.
- FES should be used as an intervention either alone or as an adjunct with other physiotherapy rehabilitation.
- Articles finding effect only in neurological conditions.
- Original studies, systematic reviews, randomized controlled trial, quasi - experimental studies, interventional studies & feasibility studies were included.

❖ **Exclusion criteria**

- Language other than English
- Published before year 2010
- Condition other than neurological condition
- Surgical approach used as an intervention

DISCUSSION

This review summarizes the evidence related to the use of FES in different neurological conditions. Many articles had strong evidence to support the use of FES for upper and lower extremity function, spasticity reduction, gait & balance improvement and so on.

According to study of Dwen A Howlett et al.[(4)] FES improves upper and lower limb activity compared with no intervention and training alone. Another study by John Eraifej et al.[(1)] proves that FES improves motor function and ADL when applied in acute phase (2 months). The reason for not improving in chronic cases might be treatment duration which was short in this study. Another outcome of BBT doesn't found significant improvement might be because of study including BBT as outcome measures was >1 year and duration for which it was treated was short. The study done by Amir K Vafadar et al.[(5)] states that FES doesn't have a significant effect on upper arm motor function early after stroke compared to conventional therapy but can be useful to prevent or treat subluxation. This study used outcome measures which were measuring impairments instead of functional assessment. Outcome measures used for subluxation were X-ray and displacement of head in cm or mm. FES improved subluxation as it directly stimulates nerve of paralyzed muscle & produce contraction in those muscles instead of conventional treatment during flaccid phase giving traditional sling and arm supports.

Table 1: Evidence of FES in STROKE

Author	Sample Design/ No of Articles And Subjects	Intervention	Outcome Measures	Result	Level of Evidence
Owen A. Howlett et al (2015)[4]	A Systematic review with meta-analysis of FES improving activity after Stroke (18 trials {8LL & 10 UL} – 15 RCT, 1CCT, 2CT including 485 patients were included)	Intervention group received FES (grasping and releasing activities for UL and gait training activities for LL) with frequency of ES 25 to 50Hz & pulse width 200 - 400µs for 20mins to 6 hrs. FES was applied for 2 to 7 sessions per week for 2 to 12 weeks. Control group received either no intervention or placebo or same activity training.	For UL: – Motor Assessment Scale – Arm Motor Ability Test – Nine Hole Peg Test For LL: – Walking speed (m/s)	FES has moderate effect on activity (SMD .40; 95% CI) compared with no or placebo intervention. It has moderate effect on activity (SMD .56; 95% CI) compared with training alone. In subgroup analyses, large effect was found on upper limb activity (SMD .69; 95% CI) & small effect on walking speed (mean diff, .08m/s; 95% CI) compared with control group.	1
John Eraifej et al. (2017) [1]	A Systematic review with meta-analysis in stroke for improvement of ADL and motor functions in upper limb. (20 RCTs of which 5 studies= <2 months, 5studies= 1-3 yrs., 6studies = >3yrs)	Intervention group received FES with a frequency of 20 – 50 Hz, peak current = ≤70mA for duration of 3 to 10s. Muscle stimulated were deltoid, triceps, wrist & finger flexors/extensors. Control group received either traditional treatment or sham FES.	Primary: ADL Secondary: Functional motor ability Tertiary: other motor outcomes	3 Studies where FES was initiated on average within 2 months post stroke showed benefit of FES on ADL (SMD 1.24 CI [0.46,2.03]; n =32). No significant result was found in other studies where FES was started after 1 year.	1
Ami K Vafadar et al. (2015) [5]	Systematic review and meta-analysis improving clinical outcomes in upper arm. (9 RCTs and 1 quasi RCT were analyzed)	Interventional group received FES in addition to conventional therapy. Supraspinatus and posterior deltoid were stimulated for 5 days/week for 4 - 8 weeks with a frequency ranging from 10 to 36 Hz. Control group received only conventional treatment.	Shoulder subluxation: – X ray – Displacement of head of humerus in cm or mm Pain: – pain during PROM of lateral rotation – NPRS Motor Function	Meta analyses showed a significant difference in shoulder subluxation in experimental groups compared to control groups, only if FES applied early after stroke. There is no any significant finding of FES to improve pain and motor function.	1
Swati Mehta et al. (2012)[6]	Systematic review improving gait in patients with chronic stroke. (7 RCTs with 231 patients)	Interventional group received FES via surface electrodes or implantable electrodes for walking. The muscle stimulated were gluteal, hamstrings, quadriceps, dorsiflexors, plantar flexors and evertors. Some studies used peroneal nerve stimulation. Frequency varied between 4 & 20mA and pulse width of 50 - 450µs.	6MWT 10MWT FIM	A small but significant treatment effect of FES was found on 6MWT (0.379±0.152; 95% CI, 0.081 – 0.677; P =.013)	1
Zhimei Tan et al. (2014)[7]	Randomized controlled trial improving gait in early stroke (4 channel FES group n = 16, 2 channel FES group n =14, placebo group n = 15 with total of 45 subjects)	All the subjects were treated in side lying position with the affected lower extremity supported by 2 slings fixed over the knee and ankle joint. Stimulation was given for 30 min per session, 1 session per day & 5 days/week for 3 weeks.	Fugl Meyer Assessment, Postural Assessment Scale for Stroke patient, Berg Balance Scale, Functional Ambulation Category, Modified Barthel Index	The score of FMA and MBI improved significantly in four channel group at the end of 3 weeks training. The scores of Postural Assessment Scale for Stroke patient, Functional Ambulation Category, BBS, MBI were significantly higher than those of placebo group. The training effects were sustained for at least 3 months after treatment.	2
Ardalan Shariat et al (2019)[8]	A Systematic review with meta-analysis of cycling with and without FES on lower limb dysfunction (14 studies)	Cycling was given as an intervention and control group was not given any treatment for the same in few studies. While other included cycling with FES in one group and only cycling in comparison group.	Berg balance scale, 6MWT, 10MWT, and other scales for measuring mobility and walking speed	Cycling had a positive effect on 6MWT compared with no or placebo intervention. Compared with control cycling had a positive effect on 10MWT, BBS. Cycling with FES had a positive effect on balance beyond cycling alone.	1

Table no 1 continued…					
Jennifer A Robertson et al. (2010)[9]	Pre and post-test interventional study on balance function and balance confidence. (15 subjects with chronic stroke)	Dorsiflexors muscle were stimulated via peroneal nerve through Velcro cuff which was attached just below the knee. Change in pressure triggers the stimulation for balance and different ambulatory techniques. Frequency of 25 Hz and 100 sec pulse width was used for 4 weeks of duration.	Activity Specific Balance Confidence Scale, Berg Balance Scale, timed up and go test, gait speed	Small but statistically improvements in gait (toe clearance) and balance function can occur during FES treatment applied to ankle dorsiflexors during swing phase of gait. Not found significant improvement in gait speed.	3
Sang Hyun Moon et al. (2017)[10]	Interventional study on effect on muscle tone & stiffness of stroke. (10 subjects)	FES on ankle dorsiflexors (Tibialis anterior) in sitting position for 30 minutes for 5 times a week for 6 weeks. Programmed used was pulse rate of 35 Hz, pulse duration of 8 sec, off pulse duration of 11 sec, pulse amplitude of 250µV	Myoton (measured muscle tone and stiffness of gastrocnemius)	For muscle tone medial and lateral gastrocnemius muscle showed significant difference of ($p<0.05$). Muscle stiffness of medial gastrocnemius ($p<0.01$) and lateral gastrocnemius ($p=0.01$) were more significant.	3

Table 2: Evidence of FES in Spinal Cord Injury

EJ McCaughey et al. (2016)[11]	A Systematic review and meta-analysis of abdominal FES to improve respiratory functions. (14 studies, of which 10 acute and 4 chronic)	Intervention was stimulation of either or both rectus abdominis muscle and external oblique muscle with 2, 4 or 8 electrodes during respiration. Mean pulse width was 259µs, frequency of 50 Hz, median maximum amplitude of 100 mA. Conventional treatment was strengthening of abdominal muscles.	Cough peak flow, PEF, FEV1, MEP, FVC, VC	Abdominal FES found a significant acute improvement in CPF, FEV1. A significant chronic increase in unassisted VC, FVC, PEF was found.	1
Anas R. Alashram et al.(2020)[12]	A Systematic review of spasticity reduction with FES cycling (10 studies: 2RCT, 2 cohort, 6 pilot)	Intervention was FES with cycling and the placement of electrodes were over quadriceps, hamstring and gluteal muscle.	Modified Ashworth Scale, pendulum test, Numerical rating scale- spasticity, Patient reported impact of spasticity measure	Significant reduction in MAS and NRS-spasticity scores ($p<0.05$) after FES cycling post treatment, and at 3 & 6 months. It is considered suitable intervention for medically stable SCI patients with an indication of lower extremity movements.	1
Anjali Sivarama-Krishnan et al (2018)[13]	A pilot randomized cross over trial of comparing TENS and FES for spasticity reduction. (10 subjects with lower limb spasticity)	One group received FES with pulse rate 35 Hz, pulse width 300µs, ramp up = 3s, hold = 5s, ramp down = 2s. another group received TENS with pulse duration of 300µs, frequency of 100Hz. Intervention was for 30 mins and single session.	Modified Ashworth Scale (hip adductors, knee extensors, ankle plantar flexors) Spinal cord assessment tool for spastic reflex (SCATS).	Between group analysis did not showed significant improvement ($p>0.05$). In within group analyses spasticity reduction was found upto 4 hrs in hip adductors& knee extensors($p<0.01$). SCATS value showed significant improvement at 1hr following TENS and 4 hrs following FES($P=0.01$)	2
Naaz Kapadia et al. (2014)[14]	A Randomized trial for walking in incomplete SCI.	Interventional group received FES stimulation while ambulating on body weight support treadmill and harness system. Muscle stimulated were bilateral quadriceps, hamstring, dorsiflexors and plantar flexors with pulse amplitude of 8 – 125mA, pulse width of 0 - 300µs and frequency of 40 Hz for 3 days a week for 16 weeks.	Functional independence measure, Spinal cord independence measure (SCIM), 6MWT, 10 MWT, Modified ashworth scale, timed up and go test, Walking mobility score, an assistive device score.	FES therapy for walking resulted in improved voluntary therapy walking function, but it was not superior to an equal dose of aerobic and resistance training except SCIM sub mobility sub score which improved in interventional group.	2
Margot Bergmann et al.(2019)[15]	A Crossover trial on trunk muscle tone and dynamic sitting balance in chronic SCI (18 subjects)	5 subjects with SCI were alternately allocated to two study groups; FES +therapeutic exercise and only therapeutic exercise. 8 control subjects were taken. FES was applied to erector spinae and rectus abdominis muscle for a period of 30 min for 6 weeks.	Myotone (muscle oscillation frequency) Dynamic sitting balance (limits of stability)	MOF in interventional group increased by 6% for ES and 6.1% for RA muscle. LOS of flexion increased 30.1% in interventional group while increase. After 7-months break period, a slight decline in trunk muscle tone and extensive decline in sitting balance value was noticed.	3

Table 3: Evidence of FES in Multiple Sclerosis

Miller et al. (2017)[16]	A Systematic review and meta-analysis for foot drop FES on impact of gait speed. (19 studies)	Peroneal nerve stimulation was used for foot drop. Some articles used surface electrodes single channel or dual channel, while some used implanted electrodes.	10-meter walk test, 25-foot walk test, gait speed over 6MWT	Short walk test showed significant initial orthotic effect (p=0.016) with mean increase in gait speed of 0.05m/s & ongoing orthotic effect (p=0.003) with a mean increase of 0.08m/s. no significant improvement in long walk test was found.	1
Linda Miller Renfrew et al. (2019)[17]	A Systematic review on health-related quality of life (8 studies)	Most articles included common peroneal nerve stimulation for foot drop, while one used gluteal stimulation in addition.	26 – item multiple sclerosis impact scale, 36 item short form health status survey, Canadian occupational performance measure, psychological impact of assistive device scale	FES has significant effect on speed and energy cost of walking & HRQOL (such as impact of MS perceived activities of daily living performance, competence, self-esteem and confidence in adults with MS)	1
Shmuel Springer et al. (2017)[18]	A Systematic review on gait (12 studies)	11 out of the 12 studies used peroneal stimulation for treatment of foot drop, & one study added a 2nd channel of stimulation activating the gluteal muscles to provide hip extension & abduction during stance phase. Surface electrodes were used in all studies.	Walking speed, walking endurance, Gait kinematics, Falls, Health status	Most found significant orthotic effect, mainly on walking speed. Only three studies assessed therapeutic effect, which was not significant.	1

Table 4: Evidence of FES in Parkinson's Disease

Livia Popa 40Hzet al (2015)[19]	A Feasibility study on bradykinesia (11 subjects)	Group 1 received stimulation of wrist, finger and thumb extensors. Group 2 received stimulation of intrinsic muscles of hand. Stimulation parameters used were frequency 40 Hz, pulse width 180µs, on time 5s, off time 5s, ramp time 2s. Both groups received common peroneal stimulation in swing phase of gait with pulse width 180µs & frequency 40Hz. Intervention was given for 2 weeks.	Walking speed, step length, cadence, Tinetti Balance score, Box and Block test, Modified Parkinson's disease quality of life questionnaire, SPES/SCOPA scale.	There was significant improvement in walking speed(p=0.002), step length (p=0.007), cadence (p=0.045), Tinetti balance score (p=0.006), BBT (p=0.025), PDQL (0.013), SPES/SCOPA score(p=0.005)	4

Table 5: Evidence of FES in Cerebral Palsy

Irene Moll et al (2017)[20]	A Systematic review of ankle dorsiflexors during walking (14 articles with 127 patients)	Surface electrodes or percutaneous electrodes were used to apply peroneal nerve stimulation with biphasic or monophasic waveform, pulse width of 3 - 350µs with varying pulse frequency.	Classified based on ICF (activity and participation level, body structure and function)	At ICF participation and activity level, there is limited evidence for a decrease in self-reported frequency of toe drag and falls. At ICF body structure and function level, there is clear evidence that FES increased ankle dorsiflexion angle, strength, motor control, balance and gait kinematics, but decreased walking speed.	1
Hsiu Ching Chiu et al. (2014)[21]	A Systematic review on activity (5 RCTs)	Experimental group received FES while performing an activity such as walking. The control group had to receive either no intervention or placebo FES intervention or activity training that was consistent with the experimental group.	Walking speed, Gross motor function measurement	3 trials reported statistically significant between group difference in favor of FES compared with no FES. 2 trials reported no statistically significant between group difference of FES compared with activity training alone.	1

Table 6: Evidence of FES in Hereditary Spastic Paraparesis

Jonathan Marsden et al.(2012)[22]	Comparative study on walking (11 subjects with SP and 11 control)	Peroneal nerve stimulation was given to interventional group. Control group didn't receive FES	Muscle torque & ankle motion, perceived efficacy, clinical outcome measures and walking kinematics	FES increases dorsiflexors torque, improves toe clearance & dorsiflexion in swing phase, and significantly improves walking speed ($p<0.05$)	3

Table 7: Evidence of FES in Foot Drop

Sarah Prenton et al. (2016)[23]	A Meta-analysis of orthotic effect (FES vs AFO) (7 RCTs)	Three trials used customized AFO, one used off-the shelf AFO, one used combination, one trial used surface FES, one trial highlighted clinicians set FES for measurement	Based on ICF domains	FES showed comparable improvements in walking speed over 10m($p=0.04$-0.79), functional exercise capacity($p=0.10$-0.31), timed up and go ($p=0.821$ and $p=0.539$) & perceived mobility($p=0.80$) for both interventions.	1

*Abbreviations

10MWT – 10 Meter Walk Test
6MWT – 6 Minute Walk Test
ADL – Activities of Daily Living
BBS – Berg Balance Scale
BBT – Box and Block Test
CCT – Controlled Clinical Trial
CI – Confidence Interval
CT – Controlled Trial
ES – Electrical Stimulation
FEV1 – Forced Expiratory Volume in 1 second
FIM – Functional Independence Measure
FMA – Fugl Meyer Assessment
FVC – Forced Vital Capacity
HRQOL – Health Related Quality of Life
ICF – International Classification of Functioning, Disability and Health
LOS – Limits of Stability
MBI – Modified Barthel Index
MEP – Maximum Expiratory Pressure
MOF – Muscle Oscillation Frequency
NPRS – Numerical Pain Rating Scale

NRS spasticity - Numerical Rating Scale for Spasticity
PDQL – Parkinson Disease Quality of Life Questionnaire
PEF – Peak Expiratory Flow rate
PROM – Passive Range of Motion
RA – Rectus Abdominis
RCT – Randomized Controlled Trial
SCATS - Spinal cord assessment tool for spastic reflex
SCI – Spinal Cord Independence Measure
SCOPA – Scales for Outcome in Parkinson's Disease
SMD – Standard Mean Difference
SPES/SCOPA – Short Parkinson Evaluation Scale
VC – Vital Capacity

Thus, FES improves subluxation in patient having stroke of < 6 months and on follow up after 4 and 12 weeks no improvement was seen. So, FES can be given to improve upper and lower extremity function in acute and chronic stages with higher treatment duration.

Gait abnormality has major affections in stroke patients. Some studies were done in acute & chronic stages finding significant improvement with FES by peroneal nerve stimulation. Swati Mehta et al.[(6)] concluded that FES improves gait speed and walking in chronic stroke patients. The study by Zhimei Tan et al.[(7)] suggest that four channel FES improves motor function, balance, walking ability, & performance of ADL in subjects with acute stroke. Ardanlan Shariat et al[(8)] concluded that FES combined with cycling has significant improvement in balance and gait. A study by Robertson et al[(9)] concluded that FES to dorsiflexors improves toe clearance, walking, turning, ascending & descending stairs, ramps, crossing obstacles, walking over different surface. There is evidence which suggest FES improves Spasticity which can be explained by its action on increased Ib fiber activation via mechanism that facilitate the Renshaw cell recurrent inhibition & on increasing cutaneous sensory stimuli. Sang Hyun Moon et al[(10)] concluded that FES improves calf spasticity.

FES improves respiratory functions, spasticity, gait, independence & balance in patient with complete or incomplete spinal cord injury in acute and chronic cases. Ej McCaughey et al.[(11)] conducted a study on abdominal FES, and found significant improvement in acute and chronic effect of respiratory functions. The acute effect of abdominal FES on CPF and FEV1 can be explained by the fact that applied stimulation increases intrathoracic pressure. The improvement in chronic effect on FVC and PEF is suggestive because of increase in abdominal muscle strength. Spasticity reduction is seen following SCI with cycling combined with FES.[(12)] One study when compared FES with TENS for spasticity reduction found significant improvement in individual group but no significant difference was seen between group, which suggest that TENS or FES can be given alternatively for spasticity reduction in lower limb which works on mechanism of reciprocal inhibition[(13)]. A study was done by Naaz Kapadia et al.[(14)] on walking competency, who found that FES improves walking function in incomplete SCI, but was not superior to an equal dose of aerobic and resistance training. FES assisted walking was found superior with respect to SCIM mobility subscore which was significantly higher. Effect of FES on balance was studied by Margot Bergmann et al.[(15)] who found the effect on muscle oscillation frequency and limits of stability in terms of muscle tone of trunk muscles and dynamic sitting balance which was statistically significant when FES was given with therapeutic exercise, but when follow up after 7 months break period, a slight decline in trunk muscle tone and extensive reduction in sitting balance values was noticed.

Strong evidence suggests that FES when applied for foot drop in patients with Multiple Sclerosis has initial and ongoing orthotic effect on gait speed in short walking test and also has significant effect on energy cost of walking and HRQOL such as impact of MS perceived activities of daily living performance, competence, self-esteem and confidence in adults with MS. Studies were done in which peroneal nerve stimulation was given for foot drop. [(16-18)]

Liva Popa et al.[(19)] conducted a study finding effect on bradykinesia in Parkinsonian patients. Modest improvement in upper limb function was noted when compared to lower limb. Some participants also noticed increased amount of walking. There is also strong evidence suggesting effect of FES is more effective for improving gait in patients with cerebral palsy than no FES intervention but has similar effect to activity training alone. FES can be used as an alternative to classic orthotic treatment. Rather than being used

routinely in clinical practice, it might be useful for those children who find exercise program difficult due to their level of disability of poor concentration or cognitive problems.[20][21]

Hereditary spastic paraparesis can lead to multiple impairments such as weakness & spasticity. Symptoms mainly affect both legs & result in difficulties with standing, balance and walking. Marsden J Stevenson[22] conducted a study finding effect of FES on dorsiflexors thereby improving walking. FES may aid walking by improving toe clearance and ankle dorsiflexion. A study done by Prenton et al[23] concluded that FES has a significant effect in patients with foot drop in different neurological condition but can be used as an alternative to ankle foot orthosis.

CONCLUSION

FES has a strong evidence to improve motor functions in upper and lower extremity, gait & ADL in stroke patients. There is also a strong evidence of additive effect of FES to improve spasticity in lower limb in stroke patients. FES has a strong evidence to improve respiratory function (abdominal FES) and spasticity of lower limb in SCI. FES also improves gait in Multiple sclerosis & Cerebral Palsy through peroneal nerve stimulation.

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