Electrophysiological Outcome Measures in Spinal Cord Injury Clinical Trials: A Systematic Review

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Background: Electrophysiological measures are being increasingly utilized due to their ability to provide objective measurements with minimal bias and to detect subtle changes with quantitative data on neural function. Heterogeneous reporting of trial outcomes limits effective interstudy comparison and optimization of treatment. **Objective:** The objective of this systematic review is to describe the reporting of electrophysiological outcome measures in spinal cord injury (SCI) clinical trials in order to inform a subsequent consensus study. **Methods:** A systematic search of PubMed and EMBASE databases was conducted according to PRISMA guidelines. Adult human SCI clinical trials published in English between January 1, 2008 and September 15, 2018 with at least one electrophysiological outcome measure were eligible. Findings were reviewed by all authors to create a synthesis narrative describing each outcome measure. **Results:** Sixty-four SCI clinical trials were included in this review. Identified electrophysiological outcomes included electromyography activity (44%), motor evoked potentials (33%), somatosensory evoked potentials (33%), H-reflex (20%), reflex electromyography activity (11%), nerve conduction studies (9%), silent period (3%), contact heat evoked potentials (2%), and sympathetic skin response (2%). Heterogeneity was present in regard to both methods of measurement and reporting of electrophysiological outcome measures. **Conclusion:** This review demonstrates need for the development of a standardized reporting set for electrophysiological outcome measures. Limitations of this review include exclusion of non-English publications, studies more than 10 years old, and an inability to assess methodological quality of primary studies due to a lack of guidelines on reporting of systematic reviews of outcome measures. **Key words:** *electromyography, electrophysiological outcome, motor evoked potential, outcome assessment (health care), spinal cord injuries, somatosensory evoked potential*

Spinal cord injury (SCI) is a devastating neurologic event that results in significant sensory, motor, and autonomic dysfunction. There has been substantial effort in testing and developing treatments to improve recovery after SCI in animals, which often fail to translate to human studies. This may largely be due to the difference in outcome measures seen in animal studies compared to human studies. Outcome measures for preclinical studies show a range of measurements, including cellular and electrophysiological changes, whereas outcomes for human trials are largely functional and behavioral.[1-3] Functional outcome measures are ultimately of most importance, but the failure to achieve impact of an intervention on a functional measure should not be fruitless. Understanding the effect of an intervention on the neurophysiology can guide future treatments that may subsequently achieve clinically meaningful outcomes. As long as this information remains unavailable, a major index in determining success or failure of a treatment will be absent, limiting the chance for a successful translation to individuals with SCI.

In contrast to the typical functional and behavioral primary outcome measures seen in human SCI clinical trials, electrophysiological (EP) measures are largely objective, independent of patient input, and unbiased in that results are not dependent on the subjective responses of patients.[4] Used in conjunction with conventional clinical

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examinations, EP examinations have developed into a complement for assessing function after SCI.[4] However, heterogeneity in reporting of EP measures (both units of measure and methods of collection) introduces bias and hampers interstudy analyses of intervention efficacy.

The methodology of collecting and reporting outcome measures is a recognized challenge in many clinical fields and has led to the development of guidelines and minimum data sets.[1-3] A first step to create guidelines and data sets is often a systematic review to identify the range of outcomes used in the literature.[1-3] The objectives of this study were to describe the range of EP outcome measures and the manner in which they are reported in clinical trials of human SCI prior to the development of guidelines on reporting of these outcomes.

Methods

The systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and registered with the PROSPERO prospective register of systematic reviews (CRD42019127713). A systematic search of PubMed and EMBASE was performed to identify relevant articles to answer the above objectives.

The initial search strategy was constructed for PubMed and adapted to the EMBASE search. We used the MeSH term "spinal cord injuries." The following search limitations (inclusion criteria) were used: clinical trials, publications between January 1, 2008 and September 15, 2018, humans, and English language. Due to the presence of many EP measures used in clinical trials and the use of various key words for such measures, the initial search intentionally used broad search terms to identify all SCI clinical trials. Electroencephalogram (EEG) and EP measures routinely performed in bowel and bladder studies were excluded because they were considered beyond the scope of this review.

Titles and abstracts retrieved by the search strategy were screened by two review authors (R.K. and M.S.) for full article review eligibility based on the identification of at least one EP outcome in response to a treatment or intervention in adult humans (>18 years age) with SCI. The full-text articles of the eligible abstracts were retrieved and assessed by R.K. and A.S. for final inclusion. A data extraction form was used for the desired information. Data elements included year, study design, population, sample size, intervention, comparison group, and outcome of interest (**Table 1**). We obtained detailed information on EP measures that included unit of measures, purpose of measurement, and methods of collection and reporting. Any discrepancies during this process were settled by consultation between two authors (R.K. and A.S.). There is no specific assessment tool or checklist available for appraisal of methodological quality of systematic reviews examining clinical outcome measures and their measurement properties. Risk of bias assessment was not performed as the primary goal was to evaluate EP outcome measure reporting. After data extraction the findings were reviewed by all authors. A descriptive synthesis narrative was prepared for each outcome measure. Descriptive statistics were used to report frequency and proportion of outcome measures. When considering the reporting method of a single instrument, proportions were presented as the percentage of studies that had used that instrument.

Results

Of the 2,030 articles identified, 64 articles met our eligibility criteria. Of these, 64 were included in this study (**Figure 1**), assessing 877 people with SCI who received various interventions and 324 people with and without SCI serving as controls. Mean sample size was 19 with standard deviation of 14. Only six studies[5-10] (9%) reported sample size justification, and 18 studies (28%) reported small sample size as a limitation. In general, we defined participants as acute SCI with duration of injury of 1 to 2 weeks, subacute from 2 weeks to 6 months, and chronic if injury duration was greater than 6 months.

Among 64 studies, we identified five types of clinical trial study designs (**Figure 2**). Hybrid study designs had both controls and crossover of interventions. Eleven (17%) controlled trials had people without SCI as controls.

Table 1. Clinical trials in SCI with neurophysiological outcome measures

	Year	Study design	Population	Sample size	Intervention	Comparison	Outcome of interest
da Silva et al[43]	2018	RCT	Chronic SCI AIS B-D	*N*=25 (I=13, C=12)	Photomodulation + PT	Placebo + PT	EMG
Piazza et al[25]	2018	Controlled trial	Chronic SCI AIS A-D + healthy controls	*N*=28 (SCI=15, Healthy C=13)	ES cycling in SCI	ES cycling in healthy controls	H-reflex
Zhao et al[44]	2017	Pre-post	Chronic SCI AIS A	*N*=8	Human umbilical cord mesenchymal cells	NA	MEPs
Allison et al[35]	2017	RCT	Chronic SCI AIS A-D	*N*=20 (I=12, C=8)	Anti-inflammatory diet	No intervention	NCS
Nardone et al[21]	2017	RCT	Chronic SCI AIS C-D	*N*=10 (I=5, C=5)	Active rTMS	Sham rTMS	H-reflex, MEPs
Vaquero et al[37]	2017	Pre-post	Chronic SCI AIS B-D	*N*=10	Mesenchymal stromal stem cells	NA	EMG, MEPs, NCS, SSEPs
Radhakrishna et al[45]	2017	RCT + crossover trial	Chronic SCI AIS A-B	*N*=45	Spinalon™ (dose escalation study with 8 groups)	Placebo	EMG
Trumbower et al[12]	2017	Randomized crossover design	Chronic SCI AIS C-D	*N*=6	Hypoxia + hand opening practices	Normoxia + hand opening practices	EMG
Osuagwu et al[46]	2016	RCT	Subacute SCI AIS B-C	*N*=12 (I=7, C=5)	BCI+FES	FES	SSEPs
Vaquero et al[11]	2016	Pre-post	Chronic SCI AIS A	*N*=12	Mesenchymal stems cells	NA	EMG, MEPs, SSEPs
Oh et al[47]	2016	Pre-post	Chronic SCI AIS B	*N*=16	Mesenchymal stems cells	NA	MEPs, SSEPs
Lynch et al[48]	2016	Randomized crossover trial	Chronic SCI	*N*=10	Acute intermittent hypoxia (AIH) + ibuprofen	AIH + placebo	EMG
Khan et al[28]	2016	Randomized crossover trial	Chronic SCI Incomplete motor	*N*=20	Endurance gait training	Precision gait training	CMR
Chhabra et al[49]	2016	RCT	Acute SCI AIS A	*N*=21 (I=14, C=7)	Autologous bone marrow stem cells	No stem cells	MEPs, SSEPs
Hur et al[36]	2016	Pre-post	Subacute & chronic SCI AIS A, B, D	*N*=14	Adipose-derived mesenchymal stem cells	NA	EMG, MEPs, NCS, SSEPs
Wang et al[50]	2016	RCT	Chronic SCI AIS A	*N*=12 (I=8, C=4)	Surgical neural release and partial scar excision + OLP transplantation	Surgical neural release and partial scar excision	H-reflex and SSEPs
Shin et al[19]	2015	Controlled trial	Acute, subacute, and chronic SCI AIS A-B	*N*=36 (I=19, C=15)	Human fetal brain-derived neural stem cells	No stem cells	MEPs, SSEPs
Zewdie et al[29]	2015	Randomized crossover trial	Chronic SCI AIS C-D	*N*=16	Endurance training	Precision training	CMR, EMG, MEPs
Gomes-Osman et al[9]	2015	Randomized crossover design	Chronic SCI AIS C-D	*N*=24	Vibration, TENS, tDCS	Vibration, TENS, tDCS	MEPs
Gomes-Osman et al[8]	2015	RCT+ crossover trial	Chronic SCI + healthy controls	*N*=21 (I=11, healthy controls=10)	rTMS+ repetitive task practice (RTP)	sham-rTMS+RTP	MEPs

Table 1. Clinical trials in SCI with neurophysiological outcome measures (CONT.)

	Year	Study design	Population	Sample size	Intervention	Comparison	Outcome of interest
Zhai et al[51]	2015	Controlled trial	Chronic SCI AIS A-D	*N*=62 (I=31, C=31)	Mouse nerve growth factor (IM) + rehab training	GM-1(IV) + rehab training	SSEPs
Estigoni et al[52]	2014	Pre-post	Chronic SCI AIS A-C	*N*=8	FES	NA	EMG
Murray et al[18]	2014	RCT + crossover trial	Chronic SCI AIS B-C	*N*=9	Anodal tDCS 1mA and 2mA	sham	EMG, F-wave, MEPs
El-Kheir et al[7]	2014	RCT	Chronic SCI AIS A-B	*N*=70 (I=50, C=20)	Bone marrow stem cells + PT	PT only	MEPs, SSEPs
Mendonca et al[10]	2014	Pre-post	Chronic SCI AIS A	*N*=14	Bone marrow mesenchymal stem cells	NA	SSEPs
Chen et al[53]	2014	RCT	Chronic SCI AIS A	*N*=7 (I=5, C=2)	OEC, SC, OEC+SC	No stem cells	EMG, SSEPs
Leech et al[54]	2014	Randomized crossover trial	Chronic SCI AIS D	*N*=10	Gait training +SSRI	Gait training + 5HT antagonist	EMG
Knikou et al[26]	2014	Pre-post	Chronic SCI AIS A-D	*N*=16	Locomotor training	NA	EMG, H-reflex
Chu et al[55]	2014	RCT + crossover trial	Chronic SCI AIS C-D	*N*=10	baclofen, tizanidine	Placebo	EMG
Hofstoetter et al[56]	2014	Pre-post	Chronic SCI AIS D	*N*=3	Transcutaneous spinal cord stimulation	NA	EMG
Shapiro et al[57]	2014	Pre-post	Acute SCI Complete injury	*N*=14	Oscillating field stimulation	NA	SSEPs
Nardone et al[58]	2014	Controlled trial + crossover trial	Chronic SCI AIS C-D + healthy controls	*N*=17 (SCI=9, healthy C=8)	rTMS	Sham stim in SCI and rTMS healthy controls	H-reflex
Fenuta et al[59]	2014	RCT + crossover trial	Chronic SCI AIS C-D + healthy controls	*N*=14 (SCI=7, healthy C=7)	Lokomat, manual treadmill, and ZeroG in SCI	Lokomat, manual treadmill, and ZeroG in control	EMG
Tabakow et al[22]	2013	Pre-post	Chronic SCI AIS A	*N*=6	OEC	NA	EMG, MEPs, NCS
Dai et al[60]	2013	RCT	Chronic SCI AIS A	*N*=40 (I=20, C=20)	Bone marrow mesenchymal	No stem cells	EMG, SSEPs
Jette et al[16]	2013	Randomized crossover design	Chronic SCI AIS A, C, D	*N*=16	Active rTMS	Sham rTMS	MEPs
Hajela et al[32]	2013	Pre-post	Chronic SCI AIS D	*N*=1	Locomotor training	NA	Flexion reflex
D'Amico et al[27]	2013	Controlled trial + crossover trial	Chronic SCI AIS A-B and non-SCI controls	*N*=13 (I=6, C=7)	Zolmitriptan	Sugar pill	CMR, H-reflex
Chang et al[6]	2013	RCT	Chronic SCI AIS A-B	*N*=14 (I=7, C=7)	CPM of ankle joints	No CPM	H-reflex
Stetkarova et al[20]	2013	Pre-post	Chronic SCI AIS A	*N*=9	ITB	NA	H-reflex, silent period
Govil et al[61]	2013	RCT	Chronic SCI AIS C-D	*N*=30 (I=15, C=15)	EMG feedback to gluteus maximus + gait training	Gait training without EMG feedback	EMG

(*continues*)

Table 1. Clinical trials in SCI with neurophysiological outcome measures (CONT.)

	Year	Study design	Population	Sample size	Intervention	Comparison	Outcome of interest
Frolov et al[62]	2012	Pre-post	Chronic SCI	*N*=20	Hematopoietic autologous stem cell	NA	MEPs, SSEPs
Trumbower et al[63]	2012	Pre-post	Chronic SCI AIS C-D	*N*=13	Acute intermittent hypoxia	NA	EMG
Kumru et al[40]	2012	RCT	Chronic SCI AIS A-D + healthy controls	*N*=52 (I=18, SCI C=20, healthy C=14)	tDCS + visual illusion	None	CHEPs
Mazzoleni et al[64]	2011	Controlled trial	Chronic SCI AIS C-D & healthy controls	*N*=10 (I= 5, C=5)	Locomotor training in SCI	Locomotor training in controls	EMG
Chang et al[24]	2011	Controlled trial	Chronic SCI AIS A & healthy controls	*N*=11 (I= 5, C=6)	Limb segment vibration in SCI	Limb segment vibration in controls	H-reflex
Houldin et al[65]	2011	Controlled trial	Chronic SCI AIS D + healthy controls	*N*=26 (SCI= 9, C=17)	Lokomat training	No training or Lokomat training	EMG
Kuppuswamy et al[17]	2011	Randomized crossover trial	Chronic SCI AIS A-D	*N*=15	rTMS	Sham rTMS	MEPs, silent period, SSR
Theiss et al[31]	2011	Randomized crossover	Chronic SCI AIS C-D	*N*=7	Riluzole	Control	Flexion reflex, H-reflex
Murillo et al[33]	2011	Controlled trial	Subacute and chronic SCI AIS A, C, D	*N*=28 (I=19, C=9)	Vibration of rectus femoris in SCI	Vibration of rectus femoris in controls	H-reflex, T wave
Adams et al[66]	2011	Randomized crossover design	Chronic SCI AIS A-C	*N*=7	BWSTT	Tilt table standing	H-reflex
Grijalva et al[67]	2010	RCT+ crossover trial	Chronic SCI AIS A	*N*=14	4 amino pyridine	Placebo	SSEPs
Hoffman et al[15]	2010	RCT	Chronic SCI AIS B-D	*N*=13 (I= 7, C=6)	Bimanual MP + SS	Unimanual MP + SS	MEPs
Kumru et al[30]	2010	RCT + crossover	Chronic SCI AIS C-D	*N*=14 (I= 8, C=7)	rTMS	Sham stim	Flexion reflex, H-reflex, T reflex
Lima et al[68]	2009	Pre-post	Chronic SCI AIS A-B	*N*=20	Olfactory mucosal cells	NA	EMG, SSEPs
Chhabra et al[38]	2009	Pre-post	Chronic SCI AIS A-B	*N*=5	Autologous olfactory mucosal transplantation	NA	EMG, MEPs, NCS, SSEPs,
Cotey et al[69]	2009	Controlled trial	Chronic SCI AIS A, B, C + healthy controls	*N*=16 (SCI=11, healthy C= 5)	Lokomat gait training + vibration to quads in SCI	Lokomat gait training + vibration to quads in healthy controls	EMG
Cristante et al[70]	2009	Pre-post	Chronic SCI	*N*=39	Stem cells	NA	SSEPs
Gorassini et al[71]	2009	Controlled trial	Chronic SCI AIS C-D + healthy controls	*N*=25 (SCI=19, healthy C=6)	BWSTT in SCI	BWSTT in controls	EMG
Adel et al[72]	2009	Controlled trial	Chronic SCI AIS A, B, C	*N*=63 (I=43, C=20)	Bone marrow stromal stem cells	No stem cells	SSEPs

Table 1. Clinical trials in SCI with neurophysiological outcome measures (CONT.)

	Year	Study design	Population	Sample size	Intervention	Comparison	Outcome of interest
Lam et al[73]	2008	Pre-post	Subacute and chronic SCI AIS D	*N*=9	Gait training with resistance	NA	EMG
Mackay-Sim et al[74]	2008	Controlled clinical trial	Chronic SCI AIS A	*N*=12 (I= 6, C=6)	OEC transplant	No transplant	MEPs, SSEPs
Beekhuizen et al[5]	2008	RCT	Chronic SCI AIS C-D	*N*=24 (6 in each group)	Massed practice + SS	MP or SS or no intervention	MEPs
Kawashima et al[75]	2008	Controlled trial	Chronic SCI AIS C-D in intervention and AIS A-B in controls	*N*=12 (cervical SCI=7, thoracic SCI controls=5	UE activity effects on LE in cervical SCI	Upper extremity activity effects on LE in thoracic SCI	EMG

Note: AIS = American Spinal Cord Injury Association Impairment Scale; BCI = brain computer interface; BWSTT = body weight–supported treadmill training; C = control group; CHEP: contact heat evoked potential; CMR = cutaneomuscular reflex; CPM = continuous passive motion; EMG = electromyography; ES = electrical stimulation; FES = functional electrical stimulation; I = intervention group; ITB = intrathecal baclofen; LE = lower extremity; NA = not applicable; MEP = motor evoked potential; MP = massed practice; NCS = nerve conduction studies; OEC = olfactory ensheathing cells; OLP = olfactory lamina propria; PT = physical therapy; RCT = randomized control trial; rTMS = repetitive transcranial magnetic stimulation; SC = Schwann cells; SSEP = somatosensory evoked potentials; SSRIs = selective serotonin reuptake inhibitors; SSR = sympathetic skin response; SS = sensory stimulation; TENS = transcutaneous electrical nerve stimulation; tDCS = transcutaneous direct current stimulation; UE = upper extremity.

Identified EP measures are presented in **Figure 3**. The most commonly used EP measures were electromyography (EMG) (*n* and %), motor evoked potentials (MEPs), somatosensory evoked potentials (SSEPs), and H-reflex. Other infrequently reported EP measures include reflex EMG activity, nerve conduction studies (NCS), silent period, contact heat evoked potentials (CHEPs), and sympathetic skin response (SSR). Only twenty-six studies (41%) considered more than one EP outcome measure.

Clinical trials that reported EP outcomes (**Table 1**) were frequently studying effects of the interventions categorized in **Figure 4**. Among 16 studies with neuromodulation intervention, seven trials studied repetitive transcranial magnetic stimulation (rTMS). Gait training interventions involved training with Lokomat, body weight–supported treadmill training, and over ground training.

Electromyography

The EMG signal is a biomedical signal that measures electrical currents generated in muscles in various neuromuscular settings, such as resting state and voluntary and involuntary contractions. The motor unit action potential (MUAP) waveform and motor unit firing behavior derived from EMG signals provide an important source of information on motor neuron and muscle pathophysiology. Invasive and/or surface electrodes are used to acquire this muscle signal. EMG signals/activity were acquired from surface electrodes placed directly on the skin in all but one study that used a concentric needle electrode.[11] The signal is picked up by the surface electrode, filtered, and amplified, and it can then be analyzed in different ways.

EMG activity was clinically assessed in 28 (44%) studies. EMG activity of muscles obtained via surface electrodes was frequently reported as mean EMG amplitude in 14 studies, followed by peak EMG amplitude in five studies and presence or absence of any EMG activity pre-post intervention in four studies. Other infrequent methods of reporting EMG results include EMG area, median frequency, and recruitment. In one study, coactivity ratio was calculated from EMG activity of agonist and antagonist muscles.[12] Three studies reported EMG activity using a combination of the above measures. Units of measures and details on EMG outcomes were absent in two studies. Given the

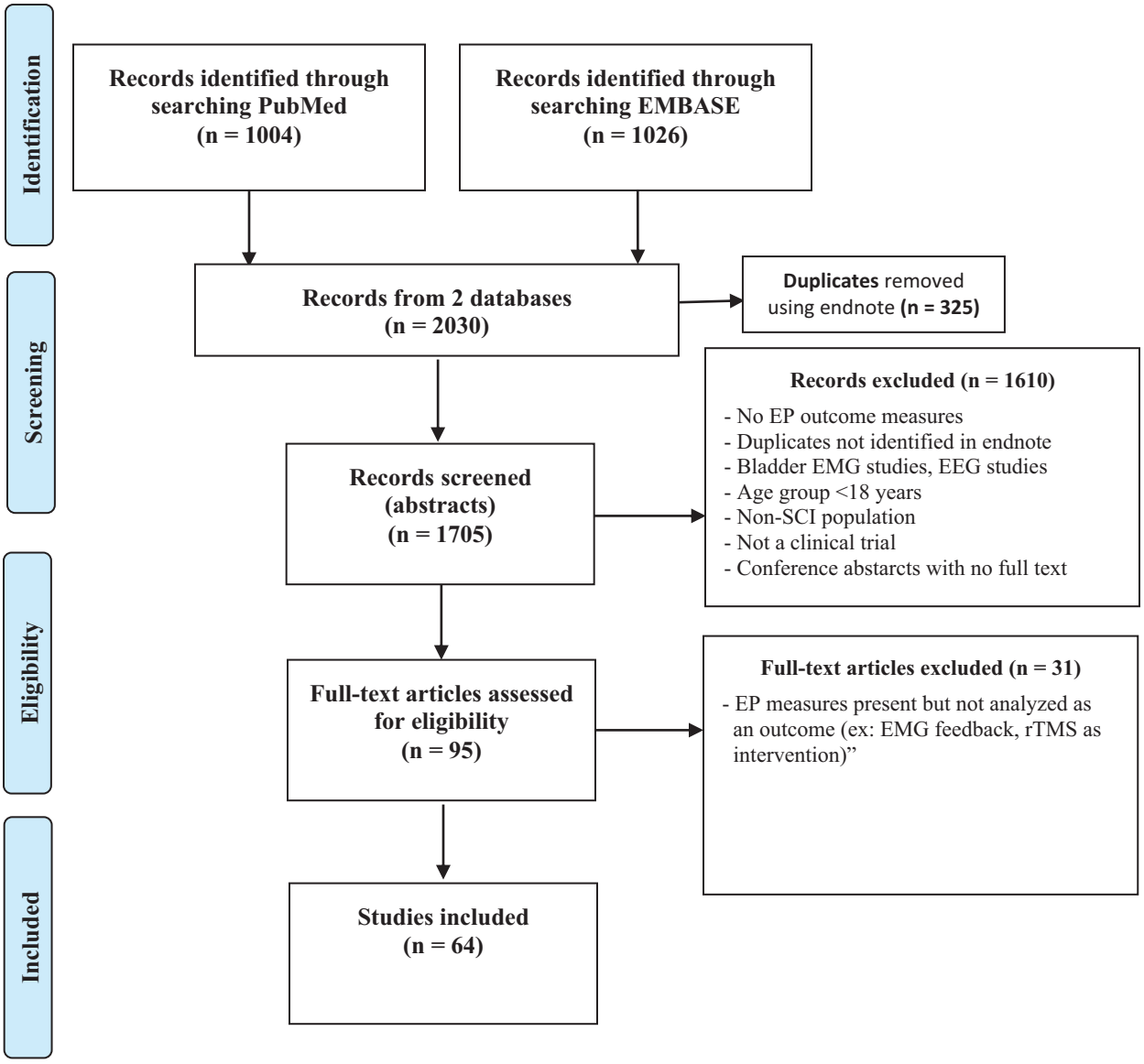

Figure 1. PRISMA flow diagram of the search strategy. EEG = electroencephalogram; EMG = electromyography; EP = electrophysiological; rTMS = repetitive transcranial magnetic stimulation.

variability in the reporting of EMG outcomes, no further analysis can be provided.

Motor evoked potentials

MEPs are muscle action potentials elicited by transcranial brain stimulation or trans–spinal cord stimulation. MEPs elicited by transcranial stimulation (invasive and noninvasive) can monitor the functional integrity of the motor pathways. Development of noninvasive methods of eliciting MEPs has become popular as a diagnostic and prognostic tool for neurological disorders.[13] Noninvasively MEPs can be produced by transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS). The clinical usefulness of TES is limited due to local discomfort produced by the high-voltage electrical stimulation to the scalp to elicit MEPs.[14] The development of TMS[13] in 1985, a new type of cortical magnetic stimulator to elicit MEPs, opened up opportunities to use it as an outcome measure.

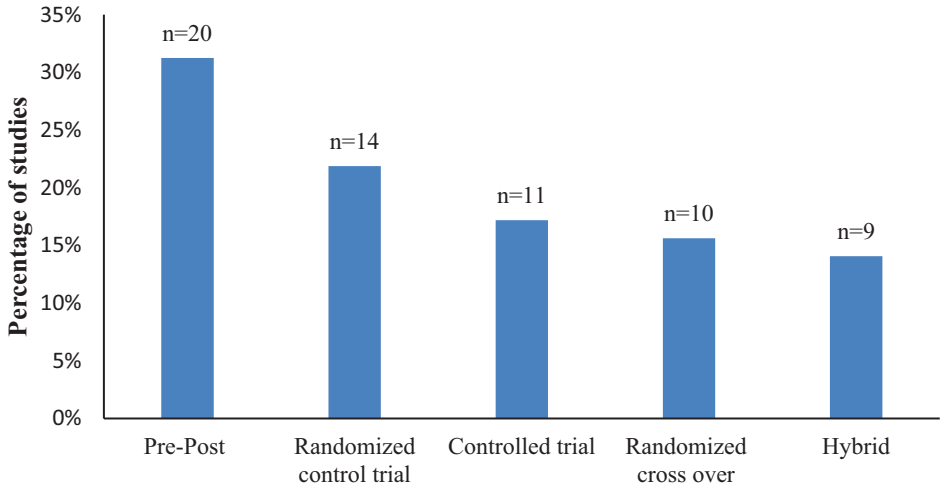

Figure 2. Types of study designs identified in this systematic review with numbers of studies above the columns

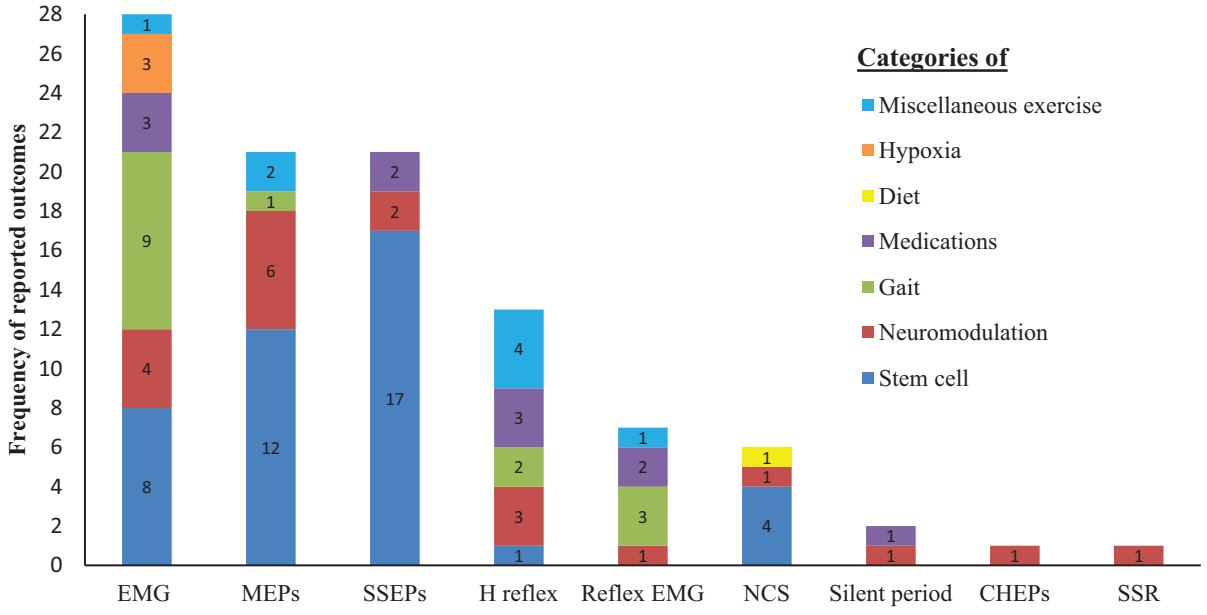

Figure 3. Frequency of electrophysiological (EP) outcomes identified. Each EP outcome has color-coded columns to illustrate the categories of research using the EP outcome. CHEPs = contact heat evoked potentials; CMR = cutaneomuscular reflex; EMG = electromyography; MEPs = motor evoked potentials; NCS = nerve conduction studies; SSEPs = somatosensory evoked potentials; SSR = sympathetic skin response.

The investigator holds the stimulating coil tangentially over the motor cortex of the target area after mapping to stimulate the cortex. MEPs are recorded with surface electrodes, which are placed over the contralateral target muscles.

MEPs were reported in 21 (33%) studies included in this systematic review. Most commonly MEPs were obtained from upper limbs; this was followed by lower limbs and infrequently from trunk in two studies. There was heterogeneity in methods and reporting of MEPs as an outcome measure. Twelve studies reported MEP amplitudes obtained at resting state or during voluntary contraction of muscle. Other

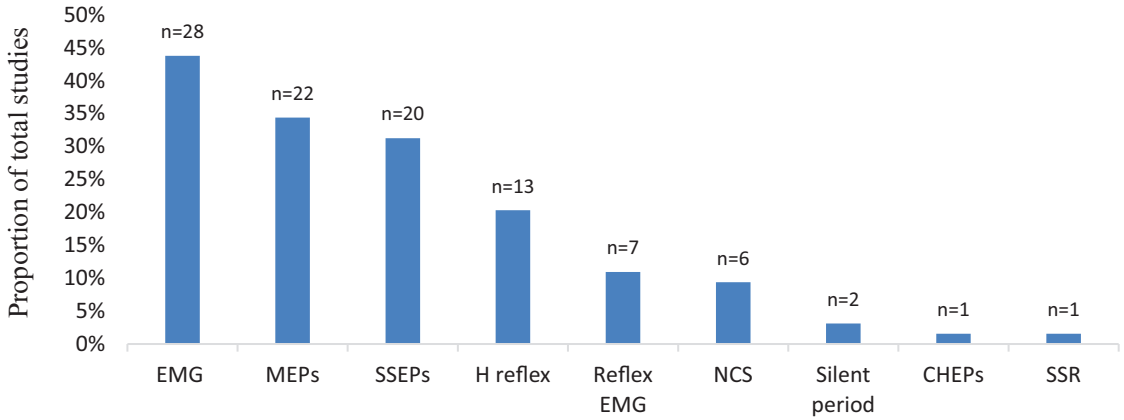

Figure 4. Types of interventions investigated in clinical trials using electrophysiologic outcomes. CHEPS = contact heat evoked potentials; EMG = electromyography; MEPs = motor evoked potentials; NCS = nerve conduction studies; SSEPs= somatosensory evoked potentials; SSR = sympathetic skin response.

MEP measures reported were MEP latencies in three studies, cortical map area in three studies, and stimulator intensity to elicit MEPs in three studies. Presence and absence of MEPs pre-post intervention were reported in five studies. Four studies only reported no change in MEPs without any further information of their methods or units of measure. Seven studies used more than one method to report changes in MEPs.

Methods of obtaining MEPs were reported in 14 (60%) studies. Seven studies obtained resting MEPs at stimulator intensity, which ranged from 1.1 to 1.4 times resting motor threshold.[5,9,15-20] Resting motor threshold was defined as lowest stimulator intensity required to produce MEPs with amplitude of at least 50 μV. Three studies reported active MEPs obtained at various percentages of maximum voluntary contraction (MVC), which ranged from 10% to 70% of MVC.[9,21] Definition of active MEPs and stimulator intensities to produce active MEPs also differed in each study. In another three studies, MEPs were elicited at intensities ranging from 40% to 100% of maximum stimulator output.[5,10,22]

Somatosensory evoked potentials

A somatosensory evoked potential (SSEP) is an evoked potential recorded with surface electrodes over the extremities, spine, and scalp, following the electrical stimulation of peripheral nerves. They provide a means for assessment of ascending somatosensory pathways. SSEPs are often performed with stimulation of the median nerve at the wrist and the posterior tibial nerve at the ankle. SSEPs evaluate the integrity of the somatosensory pathways from all levels of the nervous system: peripheral nerve, spinal cord, and brain.

SSEPs were obtained in 21 (33%) studies reported in this systematic review. Most frequently, SSEPs were measured in clinical trials by stimulation of the median nerve (n = 11) followed by the tibial nerve (n = 10). Infrequently SSEPs were obtained from ulnar nerve and para-vertebral area. Para-vertebral SSEPs were obtained to report changes in sensory level pre-post intervention. There was no information on site of stimulation to obtain SSEPs in seven studies. Reporting SSEPs included percentage of subjects with presence of SSEPs pre-post intervention in 10 studies, latencies in seven studies, and amplitudes along with latencies in two studies. SSEPS were mentioned as outcome measures in two studies, but no results were reported.

H-reflex

The Hoffmann reflex (H-reflex) is an electrically induced reflex that bypasses the muscle spindle.[23] H-reflex is a useful measure to assess modulation of monosynaptic reflex activity in the spinal cord and is used as an estimate of alpha motoneuron (α MN) excitability. It is elicited by selectively stimulating the Ia fibers of the posterior tibial or median nerve. H-reflex can be used to evaluate various

neurologic conditions, musculoskeletal injuries, and application of therapeutic intervention.[23] The H-reflex amplitude is highly variable under different conditions; therefore different methods have been used and recommended for normalization such that comparisons can be made within and between subjects.

In this systematic review, 13 SCI clinical trial studies (20%) obtained H-reflex as one of the outcome measures. All but one study reported H-reflex obtained from the soleus muscle by tibial nerve stimulation. The one exception did not provide any information on which nerve and muscle were used to obtain the H-reflex. The most common method of reporting H-reflex was the ratio of maximum H-reflex to maximum compound muscle action potential (CMAP) amplitude, known as Hmax/Mmax (n = 8, 62%). Other methods of reporting included conditioned H-reflex amplitude, homosynaptic depression of H-reflex, and recruitment curves. Four studies[6,24-26] reported H-reflex post activation depression at various frequencies by comparing H-reflex amplitudes pre and post intervention.

Methods to normalize and collect H-reflex varied as well. In addition to the Hmax/Mmax ratio for normalization, the following alternatives were used for normalization. Soleus H-reflex conditioned by peroneal nerve stimulation and plantar stimulation was obtained respectively in studies by Knikou et al[26] and Piazza et al.[25] Stimulation intensities to obtain H-reflex were adjusted with reference to Mmax for normalization in four studies.[6,24,26,27] Only one study obtained H-reflex at an intensity to evoke 50% of Hmax for normalization.[25] In all of the 13 studies, H-reflex amplitudes were compared.

Reflex EMG activity: In seven studies (11%), reflex EMG activity was measured from target muscles using surface electrodes in response to cutaneous stimulation. We found that authors used different nomenclature to report this reflex activity.

Cutaneous muscular reflex (CMR): Three studies[27-29] reported it as CMR, which was evoked by electrical stimulation of tibial nerve behind the medial malleolus or median arch of foot.[27-29] EMG activity was collected from target muscles using surface electrodes. *Withdrawal reflex activity* or flexion reflex was evoked by electrical stimulation of the medial arch of the foot to produce a TA EMG response in two studies[30,31] and by stimulation of sural nerve in another study.[32] *T-reflex* or *T-wave* was recorded from soleus muscle after tapping the Achilles tendon in two studies.[30,33] Reflex EMG was commonly reported as mean EMG amplitude.

Nerve conduction studies (NCS): NCS are obtained by electrical stimulation of sensory and/or motor nerves, with responses collected from surface electrodes or cutaneous or muscle targets, respectively. NCS provides information on conduction properties of examined nerves and assists in diagnosis of peripheral nerve disorders.[34]

Six studies (9%) included in this systematic review reported NCS including F-waves as an outcome measure. Sensory and motor NCS were obtained from various peripheral nerves. Conduction velocities were compared in four studies,[22,35-37] and additionally CMAP amplitudes were compared in two of these studies.[22,35] In one study, the NCS was reported as no change in NCS pre-post intervention without any further details.[38]

F-wave is a late response that follows the motor response and is elicited by supramaximal electrical stimulation of a mixed or a motor nerve.[34] Various F-wave parameters are used for diagnostic evaluation of peripheral nerve disorder. Only one study reported F-waves. In this study, F-wave was obtained from extensor carpi radialis muscle by radial nerve stimulation to study the effects of transcranial direct current stimulation (tDCS) on spinal excitability. Results were reported as the number of times F-wave was present during 20 stimuli.[18]

Cortical and cutaneous silent period: Cortical silent period (SP) is the interruption of EMG activity following a suprathreshold cortical magnetic stimulation. The duration of the cortical SP is a measure of intracortical inhibition due to gamma-aminobutyric acid B (GABA B) receptor-mediated inhibition of cortical excitability.[39] There is strong evidence that the mechanisms responsible for the cortical SP have functional relevance.

One study obtained cortical SP from right abductor pollicis brevis muscle during near-maximum voluntary contraction following

contralateral TMS at 140% of resting motor threshold.[20] In another study[17] cortical SP was obtained at an intensity 20% below active motor threshold during a 10% MVC from first dorsal interossei, thenar, and ECR. In these studies, duration and latency of cortical SP were compared. The cutaneous SP is a brief transient suppression of the voluntary muscle contraction that follows noxious cutaneous nerve stimulation due to suppression of activity in spinal motor nuclei. Only one study[20] reported cutaneous SP obtained from stimulating cutaneous nerves in the index fingers and collected from abductor pollicis brevis. Onset latency, end latency, and duration were measured.

Contact heat evoked potentials (CHEPs): CHEPs provide an objective evaluation of small fiber function and have been used to study neuropathic pain.[40,41] CHEPs are obtained by a heat stimulus of 32°C to 51°C over the skin. The resulting evoked potentials can be recorded and measured from sensory cortex Thus, amplitudes and latencies are obtained, being utilized to detect small fiber alterations in neuropathic pain patients. CHEPs were reported in a study to record response of tDCS combined with visual illusion on neuropathic pain by Kumru et al.[40] Thermal stimuli were delivered at the fastest available ramp rate of 70°C/s from a baseline temperature of 32°C to a maximum of 51°C over C4 sensory dermatome. Latencies and amplitudes were compared.

Sympathetic skin response (SSR): SSR represents a potential generated in the skin sweat glands; it originates by activation of the reflex arch with different kinds of stimuli. SSR is most frequently used in diagnosing the functional impairment of nonmyelinated postganglionic sudomotor sympathetic fibers in peripheral neuropathies. SSR has been proposed as a noninvasive approach to investigate the function of the sympathetic system.[42] Only one study reported SSR in response to rTMS.[17] In this study, SSR was obtained from surface electrodes from the palm and dorsum of the hand. SSR was elicited by applying magnetic stimulation to the back of neck at 65% of maximum stimulator output. The waveform, frequency of occurrence, latency, and amplitude of SSR potentials were measured.

Discussion

To our knowledge, this is the first systematic review of the SCI clinical trials literature that used EP outcome measures. Although EP outcome measures provide objective evaluation, we found substantial variation in the types of outcomes assessed, methods to collect data, and how they are reported. Key EP measures in SCI clinical trials include EMG activity, MEPs, SSEPs and H-reflex. Very few studies considered them all. The review demonstrates heterogeneity with regard to methods of measurement and reporting of EP outcome measures. Sample sizes in these studies were small, which was often reported as a limitation. Only 6 of 64 studies reported sample size justification. Heterogeneity of outcome reporting is recognized to challenge interstudy comparison and is likely to lead to bias in the dissemination of knowledge. To overcome these challenges, the development of standardized reporting of EP outcome measures is critically important. Beyond demonstrating heterogeneity, this study aimed to collate current reporting practice to assist stakeholders in developing guidelines for reporting EP outcome measures. To this end, the findings from this study provide a starting point for the development of standardized reporting of EP outcome measures. It is alarming that in many studies neither details on methods of EP outcome assessment nor EP data elements were reported. To overcome these challenges, we propose the development of standardized reporting guidelines. The findings of this study provide a basis for the development of a standardized reporting of EP outcomes measures in SCI clinical trials. We propose the use of Delphi method to develop consensus on standardized guidelines for collecting and reporting of EP outcomes in SCI clinical trials. The Delphi method is a process of arriving at group consensus by providing experts with rounds of questionnaires and the group response before each subsequent round. The results of this study could be used in the development of such a questionnaire, for example, What parameters (amplitude, latency) should be reported for a given neurophysiological test? What should be the optimal stimulator intensity to obtain MEPs? After standardizing EP collecting and reporting, further studies could help

determine the effect size for each EP outcome to reflect meaningful changes.

This review also provides information on currently available EP measures that can complement clinical exam and provide more accurate objective changes in the nervous system after SCI. No single outcome measure can be applied to all people with SCI to detect changes or monitor progress. Currently available functional outcome measures are limited, especially during early recovery of SCI. Thus, carefully tracking neuromuscular changes using EP assessments after SCI is important in assessing clinical treatment effect. EP measures could help assess changes in the spinal cord that cannot be assessed with clinical exam. Thus, EP measures may play a role in SCI outcome predictions. However, the first step is to standardize collecting and reporting methods in order to make clinically meaningful assessments.

Limitations

The search strategy excluded non-English articles. The global representation of included studies suggests that the non-English exclusion is unlikely significant. Publications older than 10 years were not included based on the argument that there has been a paradigm shift regarding the evaluation of the EP outcome measures. The authors propose that assessment of the last 10 years of published data is representative of current practice. We also noted that some studies were not captured by this search when we used the "clinical trial" filters in PubMed and EMBASE. To allow replicability and consistency of methodology of our search strategy, we did not include those studies that we found randomly. In this systematic review, we did not assess methodological quality of primary studies due to lack of standardized guidelines and check lists for systematic review on outcome measures.

Conclusion

This systematic review provides a comprehensive synthesis of evidence regarding the utility of EP measures in SCI clinical trials. EP outcomes are applicable to every type of patient regardless of their neurological level and type of injury. EP outcomes are a valuable, sensitive, and objective outcome measures in SCI clinical trials that can be applied to all levels of SCI to measure both upper and lower extremity function as well as outcomes that are currently limited. However, significant heterogeneity exists in the outcome reporting of studies assessing treatment of SCI. The development of standardized reporting of EP outcome measures would support the field in the future. The findings from this study should be used to inform a larger consensus process to define the core EP outcomes and data elements in SCI research. The continued understanding and development of existing EP measures will ensure the field of SCI research will be well-positioned to assess the efficacy of emerging interventions and the impact on function.

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