A Longitudinal Retrospective Study of a Wearable Neuromuscular Electrical Stimulation (NMES) System Shows Significant Improvement of Arm Usage in Hemiparetic and Hemiplegic Patients

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Abstract

Background

Hemiparesis and hemiplegia are commonly observed motor consequences of brain injury and infarction. Brain disorders such as traumatic brain injury (TBI), stroke (cerebrovascular accident, or CVA), and cerebral palsy (CP), as well as surgical interventions, can result in aberrant motor function in the contralateral upper and lower limbs, resulting in paralysis, weakness and/or spasticity in the arm and leg. NMES has been previously used to stimulate affected muscle groups and to increase arm mobility in a variety of brain and spinal cord diseases, yet there remains a paucity of longitudinal evidence examining NMES-mediated improvements in arm usage after brain compromise.

Methods

In this retrospective cohort study (n = 38), we examined longitudinal (up to 10 years) self-reported arm usage in patients with 1) TBI, 2) stroke, 3) prior hemispherectomy, or 4) cerebral palsy who wore an NMES device, Axiobionics’ BioSleeve, and we compared this to arm usage achieved from years of conventional therapy (physical and occupational therapy) prior to use of the wearable NMES device in this study.

Results

We found that the patients saw an average increase in arm usage from 9.9–43.5% by the end of the study. This result was well represented across age groups and genders, with varying degrees across different diagnoses. Specifically, the TBI subcohort had a consistent increase in arm usage of 5.5% per year over the term of treatment.

Conclusion

This study supports the literature identifying NMES as a therapeutic intervention and complements the literature suggesting that NMES application can be used as a long-term method to increase arm usage in hemiplegic patients.

Background

Cortical Diseases Linked to Motor Impairments

Hemiparesis (partial motor loss) and hemiplegia (total motor loss) are the reduction or inability to move the affected limbs on one side of the body and occur for a multitude of reasons. TBI, cerebral palsy, hemispherectomy, and stroke are independent underlying causes of impaired contralateral hemiparesis and hemiplegia, including a reduction in arm usage. Impaired arm positioning negatively affects arm
usage and activities of daily living (ADL), such as grooming, eating and reaching for objects (Figure 1). Therefore, increasing arm usage remains a key therapeutic goal to facilitate recovery after these disorders.

TBI is a leading cause of long-term disability among children, young adults, and the elderly in the United States. Previous work estimated that 3.3 million Americans are living with TBI-related disability (1). TBI is often a complex disorder acquired from an external mechanical force to the cranium that is of sufficient magnitude to cause temporary or permanent brain tissue damage related to neuronal or axonal damage. TBIs can be classified as mild, moderate, or severe (2, 3). Broadly, there are four types of traumatic brain injuries: 1) Concussions, 2) Brain Contusions, 3) Penetrating Brain Injuries, and 4) Anoxic Brain Injuries. This study focuses on contusion injuries sustained due to mechanical injury to the left- or right-hemispheric motor cortex because of automotive accidents. One possible outcome, depending on the severity of insult and damage to the motor cortex, is partial or complete paralysis to the contralateral upper limb muscles. Previous attempts to increase arm mobility have included singular approaches or combinations of pharmaceutical interventions, physiotherapy and electrical stimulation (ES). An analysis by Hillier (1997) estimated that long-term upper limb motor dysfunction occurs in 30% of TBI patients (4). Approaches to addressing functional impairment have focused on pharmaceutical interventions such as baclofen or therapeutic modalities such as exercise. Current work examining the usage of NMES on TBI motor recovery has produced inconsistent results (5).

Along with TBI, stroke is a leading cause of mortality and disability worldwide. Strokes can affect a variety of brain regions due to thrombotic, embolic or hemorrhagic infarcts, wherein affected regions experience lowered glucose and oxygen supplies resulting in inflammation, excitotoxicity, reactive oxygen species (ROS) release, necrosis and neuronal death. The middle cerebral artery (MCA) provides nutrients and oxygen to the motor cortex; subsequently, MCA infarcts are often associated with contralateral motor impairments, paresis, facial droop, and other abnormalities (6, 7). One study showed that motor function in the arm is aberrantly affected in 65% of stroke patients (8).

Pediatric conditions such as cerebral palsy and epilepsy-related hemispherectomy also result in contralateral motor impairments (9, 10). Cerebral palsy occurs in approximately 0.2% of births (9) and is associated with abnormal prenatal brain development (11). Affected infants commonly exhibit spasticity and motor abnormalities along with cognitive impairments. One approach to controlling intractable epilepsy includes neurosurgical interventions to excise or disconnect seizure origin (12). The use of hemispherectomy (removal of one hemisphere of the brain) and hemispherotomy (localized disconnection and targeted removal of brain tissue) can reduce the occurrence of seizures but is also
associated with contralateral motor deficits. Due to the small body size and brain size of infants and toddlers, both procedures can be complicated and risky (13).

In all aforementioned brain conditions, motor cortical activity is impaired or ablated. The motor cortex is the area of the brain responsible for the initiation, planning and control of movement. When the motor cortex is damaged, partial or complete paralysis ensues, muscle tone is altered, muscle activity diminishes, spasticity occurs, and atrophy and weakness set in (14). Impairment of the motor cortex due to cerebral palsy, TBI, stroke or hemispherectomy leads to hemiparesis or hemiplegia where the opposite side of the body is partially or completely paralyzed (7, 15-23). The motor network in the brain consists of the primary motor cortex, lateral premotor cortex, supplementary motor area, and subcortical areas such as the basal ganglia, thalamus, cerebellum, and brainstem nuclei. Injury to these regions or changes in the white matter fiber tracts that connect these regions can damage the synergistic control of the motor network and thus affect muscle function of a patient's limbs.

**Motor Control Pathways**

Controlled upper extremity movement is a synchronized neurocognitive and sensory process that begins in the planning stages in the premotor cortex and is executed by the primary motor cortex (M1). Injuries to the motor cortical areas are associated with impaired motor control and movement. Affected skeletal muscles atrophy (24, 25) or weaken even when remnant neurological control exists. Movement can diminish or vanish entirely because the atrophied muscles (Figure 4) no longer generate sufficient force to move the limb or to overcome its weight (26).

A second orthopedic problem associated with paralysis is joint stiffness and reduced range of motion (27, 28) arising from limbs staying in one position over an extended period. This condition is exacerbated by the presence of hypertonicity (29) in certain muscle groups, causing them to remain in a state of spasm (or sustained contraction), further limiting joint motion. Reduced range of motion in the upper limb diminishes arm function, and considerable effort in rehabilitation is needed to reverse the loss of mobility with limited success (30-34).

As a result of brain injury or insult, the UMN projections are unable to normally activate the LMN (35), which results in a loss of bilateral upper- and lower-limb movements (quadriplegia), loss of bilateral lower limb movements (paraplegia) or a reduction in unilateral upper- and lower-limb movement (hemiplegia) or
weakness (hemiparesis). These abnormalities result in a diminished ability to volitionally activate motor units (36) or changes in the motor units themselves, such as changes in mean twitch contraction time (37) (Figure 3). In the upper limb, the combination of paresis, loss of fractionated movements, flexor hypertonia, and somatosensory abnormalities often manifests as difficulty extending the elbow and opening the hand in a functional manner, which severely limits the ability to perform necessary functions (38-41). Therefore, any therapeutic intervention that improves upper limb movement is valuable in the field of neurorehabilitation of brain infarct patients. One such therapy for reducing hemiplegia is electrical stimulation (ES).

**Neuromuscular Electrical Stimulation (NMES) and Hemiplegia**

Neuromuscular electrical stimulation (NMES) can be used to activate muscle groups with the goal of addressing the weakness or paralysis associated with CNS injury (42, 43). The stimulus used during NMES is not sufficient to directly cause muscle contraction. Instead, during surface NMES, two or more gel-attached electrodes are placed on the skin and are used to send electrical impulses to the descending lower motor neuron pathways to activate targeted muscles, causing contraction (Figure 2). While a few studies have attempted to test NMES in clinical settings, these studies have produced inconsistent results related to a variety of factors, including lack of control groups, inconsistent experimental parameters and experimental bias (44). Therapeutic stimulation variables included frequency, dosage, waveform, amplitude, ramp time, duty cycles and electrode placement. NMES has been used as an intervention for the treatment of motor abnormalities related to various brain dysfunction syndromes, including stroke, TBI and cerebral palsy. However, to our knowledge, little work has been done to track patients longitudinally past early treatments (44).

A systematic analysis by Freitas et al. (2018) identified five studies that met acceptable standards of clinical work to appropriately test the applicability of NMES as a therapeutic modality in the treatment of upper- and lower-limb muscle weakness in CNS disorders, although this work focused on spinal cord injury (30, 45-48). Of these five, the two higher quality studies show conflicting results. Harvey EA (2010) enrolled SCI patients into two arms – a control (no intervention) and an experimental arm (NMES). They found that the experimental group showed increased voluntary strength in the quadriceps muscle after a 24- to 96-month intervention wherein participants were exposed to a 50 Hz frequency, 300 µs pulse width, 100 mA intensity and a 12:12 s ratio for 3 days/week, performing 12 series and 10 repetitions/day (49). On the other hand, work by Glinsky EA (2009) showed no difference in wrist muscle strength under similar parameters, with two key differences: a shorter total intervention time (~5 months vs. 24-96 months) and a lower intensity of stimulation (70 mA with a 6:6 ratio versus 100 mA with a 12:12 ratio) (45). Another key difference in the two studies was the population sampled: Glinsky’s study population enrolled
tetraplegics, whereas Harvey’s study enrolled both hemiplegic and tetraplegic patients. Altogether, these two high-quality studies have not yet settled the question about the applicability of NMES to muscle recovery after brain and/or SCI insult.

Although the question of whether the long-term usage of NMES reverses the loss of mobility associated with hemiparesis remains unanswered, NMES has been shown to produce inconsistent short-term improvements in arm usage in acute and subacute hemiplegic patients (50-53). Rosewilliam et al. (2012) showed that the extent of recovery was dependent on continual NMES intervention (52). In an interventional study (Tashiro et al., 2019), 23 stroke patients with severe upper limb hemiplegia underwent 3 weeks of daily NMES therapy supplanted with electrophysiological intervention (54). The daily NMES intervention produced improvements in motor function and proprioceptive feedback but not somatosensation. Fujiwara et al. (2015) performed a similar interventional study to demonstrate that NMES combinatorial therapy improved upper extremity motor function in patients with hemiparesis (55). While other studies demonstrate the potential suitability of combinatorial approaches (56, 57), the studies are heterogenous in their methods and interpretation (58). An additional consideration is the financial, logistical, and temporal burdens placed upon the patient when additional outpatient and invasive interventions are used. Therefore, there remains a need for an at-home intervention to improve motor impairment associated with brain infarcts. Previous work has shown a beneficial effect of the home-based motor training program on motor function in patients with stroke, which was accompanied by enhanced interhemispheric functional connectivity of the M1 areas (59).

The question, then, is as follows: can function be regained in patients with hemiplegia after initial recovery? In a study of TBI patients assessing neuromotor function longitudinally, Walker and Pickett concluded that patients make their largest gains in function in the acute phase but over time that leveled off by the 12th month and about a third had persistent impairment at 2 years (60).

Wearable NMES devices can, prima facie, be used to facilitate the at-home improvement of brain-insult-related motor impairments by re-educating muscles lacking proper cortical control. Axiobionics’ wearable BioSleeve muscle stimulation is such a device. The objective of this paper is to analyze the outcome data obtained from using the upper extremity BioSleeve muscle stimulation system in hemiplegic patients to gain insight into the muscle re-education process. This paper does not present data on the mechanism of action of how muscles are re-educated; it asks two critical questions. 1) Does use of the upper extremity BioSleeve muscle stimulation system help to increase arm usage beyond what was achieved in standard therapy; 2) To what extent can function improve?

Methods
BioSleeve Device and Patient Protocol

Patients with hemiparesis and hemiplegia were fitted with an Axiobionics custom upper extremity BioSleeve (Figure 5). The BioSleeve comprised six electrodes, with 2 BioGel Velcro electrodes over the deltoid, 2 over the triceps, and 2 over the finger extensors on the affected limb (Figures 3 and 5). The sleeve was designed to overlay the three muscle groups from the shoulder to the wrist. Each hemiparetic and hemiplegic patient was outfitted with a BioSleeve on the affected extremity with embedded wires and electrodes fastened to the interior of the garment with a hook and loop fastener. Electrode position was determined by the clinician at the time of the device initial fitting and was placed over the motor point of the targeted muscles. Electrode position was adjusted over time if needed to improve contraction force, to reduce discomfort, or to reduce unwanted joint deviation. Deltoid electrodes were placed over the anterior and posterior deltoid so that stimulation would contract all three heads of the deltoid (anterior, middle, posterior). The triceps electrodes were placed over the midline of the triceps with one placed proximally and one placed distally (Figure 5). The finger extensor electrodes were positioned with one electrode proximally and one distal to the proximal electrode. Every effort was made to produce finger and thumb abduction with as little wrist extension as possible and with minimal to no radial or ulnar wrist deviation. If wrist extension was more pronounced than finger extension, a static wrist-hand orthosis was applied to maintain wrist neutrality in the sagittal plane. The intensity of stimulation delivered to each muscle minimally varied between patients.

Stimulation levels were not designed to produce maximum contraction force. Rather, the level of stimulation was limited to an intensity that delivered the maximum range of motion at a particular joint without overextending the joint. For the deltoid, intensity was chosen when the humerus abducted 5-10 degrees, or if the humerus was subluxated, the intensity was determined by the amount of stimulus needed to fully approximate the glenoid fossa. This was confirmed by palpation of the space between the acromion and the head of the humerus before and during stimulation. Stimulation was applied to the triceps until the elbow extended to its endpoint. Not all elbows were able to achieve full extension when a flexion contracture was present. If spasticity was present in the biceps, the intensity was set to overcome the flexion force of the biceps without aggressively forcing the elbow into extension. The level of intensity for the finger extensors was determined when the fingers fully extended or reached their endpoint if restricted by joint stiffness or contracture. The finger extension force was kept low to moderate. Care was taken not to forcefully extend the fingers. If the stimulus intensity reached a level that triggered spasticity in the finger flexors, the intensity was adjusted to induce extension but not spasticity. The levels of stimulation required were labeled on the front face of the stimulator for patient reference. The patient was instructed to input the number for each channel every time the system was applied. Some variation in stimulus output was allowed to minimize/eliminate discomfort or to produce a slightly stronger muscle force to achieve the desired joint range of motion and limb movement. Stimulus parameters other than
current intensity were kept consistent across all patients as follows: 1) Stimulus ON Time: 10 sec, 2) Stimulus OFF Time: 10 sec, 3) Frequency: 50 Hz, 4) Pulse Width: 300 µsec, 5) Ramp Up: 3 sec, 6) Ramp Down: 2 sec. These parameters are consistent with other studies utilizing NMES for recovery (51, 61, 62).

Patients were provided a protocol to follow, including an acclimation protocol to slowly build the stimulation time from 30 minutes up to 12 hours. Patients were asked to wear the Bio Sleeve on day one for 30 minutes during the first half of the day and then another 30 minutes during the second half. They were instructed to increase the 30-minute sessions by 10 minutes every day thereafter up to 12 hours per day, if tolerated. Wear times of 12 hours were not mandated. Patients were encouraged to wear the BioSleeve 5-7 days per week or as much as tolerated but never past a point that would cause discomfort or pain.

Retrospective Cohort

The retrospective study included 38 patients (24 males, 63%, and 14 females, 37%) who were referred by a physiatrist, physical therapist, or occupational therapist or who came by self-referral to the Axiobionics clinic for a BioSleeve. All patients were treated by and reported results to the same clinician. During the evaluation visit (before the BioSleeve was fitted), the clinician verbally asked the following question to establish baseline arm usage: “What percentage of time are you using the affected arm in your own environment?” Additional clarification was given that arm activity included any activity, whether the affected arm was used by itself or as an assist to the unaffected arm. This question was not intended to discover and report function; rather, it was seeking the amount of time spent in each activity in which the affected arm was used. No distinction was made to distinguish between arm usage in and out of the BioSleeve. The same question was asked during each subsequent follow-up visit after the BioSleeve was fitted. The clinician provided additional verbal guidance by explaining that 0% meant the arm wasn't used at all and 100% meant the arm was used in a normal fashion as it would before hemiplegia took place. The clinician also recorded whether the patient was using the BioSleeve device and, if so, recorded the patient-reported number of hours the BioSleeve device was used per day. Parents or guardians of patients under the age of 18 years old or those who could not comprehend the question due to cognitive deficits were asked to report for the patient. The data were recorded in the patient chart at the time of the patient visits and extracted for the purpose of this retrospective study.

Inclusion Criteria: Hemiparesis and hemiplegia patients seen by the examiner from 2012 to 2021 for traumatic brain injury, stroke, cerebral palsy and hemispherectomy (> 3 months postinjury) who were treated with the Upper Extremity BioSleeve Muscle Stimulation System stimulating the deltoid, triceps and
finger extensors and who were able to understand and answer the home arm usage question at initial evaluation and subsequently on follow-up were reviewed for inclusion in this retrospective analysis if they were seen for at least one follow-up visit no less than 2.0 months after the initial fitting. Age was not a determining factor in the inclusion criteria. Children whose parents were able to understand and answer this same question were included in this analysis.

**Exclusion Criteria:** Patients were not included in this retrospective analysis if they or their parents or guardians were not able to report arm usage. Patients who received a BioSleeve that stimulated muscle other than the deltoid, triceps, and finger extensors were excluded from the study. Additionally, patients were excluded from treatment if they had a cardiac condition that necessitated the implantation of a demand cardiac pacemaker or defibrillator. Pregnant women (safety of muscle stimulation during pregnancy is not known), patients with dementia, patients with severe receptive or global aphasia that confounded testing and training (operationally defined as a likely inability to understand the protocols and procedures, as judged from an inability to follow commands) and patients with active cancer were excluded from treatment. Patients who had sustained cerebral injury in the past 3 months were also excluded.

**Statistical Analysis**

The statistical evaluations were carried out with the statistical program R (Version 3.1, R Foundation for Statistical Computing, Vienna, Austria). Continuous measures are represented by the means and standard deviations, and discrete features are represented by absolute frequencies. For the statistical analysis, normality was determined using the Shapiro–Wilk test. To model changes, for example, in success rates or complication rates, generalized logistic regression with a logit link function was used. The parameter significance of the generalized linear models was calculated using the Wald test (63), with the null hypothesis that the parameter was 0. A parameter was considered significant if the p value of the test was less than $\alpha=0.05$. Given the number of possible variables that could explain the outcome, the best model that explained the outcome was selected, relying mainly on stepwise regression to identify the model.

Stepwise regression was assessed using the Bayesian information criterion (BIC) of the model, where a higher BIC indicated that the factor combination of the model was a better model. To evaluate the best combination of factors, we iterated through the model, starting from the full model (i.e., including all independent variables that we intended to study). Variables were then randomly dropped to evaluate the BIC. If the BIC of the new model was higher than that of the current model, then we utilized this combination of variables for the next comparison. Randomly every n step, we added a random variable back of the set of variables that was dropped to find better forward models. We continued to iterate until we were unable to make improvements to the BIC of the model. For the final model, we selected the
model that best fit the data we had. A power calculation for the study was performed by simulating sampling from a statistical distribution representing the effect measured with the same sample size while measuring the probability of having a significant outcome (<0.05). The resulting power was then defined as the percentage of time we obtained the significant result under the same sample size and the uncertainty in the statistical distributions.

Table 1: The current cohort of patients was tested for differences between diagnosis, disease onset age, gender, and number of therapy years - either conventional or BioSleeve. This was to identify if there were statistically significant differences between the groups along with the statistical power of the tests. There were significant differences in age of disease onset, BioSleeve age, and conventional therapy years across diagnoses. The cohort does not show significant differences in gender or BioSleeve years. See Supplementary Figures 1-5.

Results

BioSleeve is Associated with a Significant Increase in Arm Usage

We found that the BioSleeve intervention significantly increased arm usage compared to baseline within our cohort (Figure 6), and we observed differences between various diagnoses (Figure 7). An initial generalized linear model was used to model arm usage against patient age, gender, period of treatment, method of treatment, and diagnosis. The method of treatment was assumed to be either conventional or BioSleeve, assuming that any prior treatments to the BioSleeve were conventional treatments. The conventional treatment period was the period from disease onset to fitting of the BioSleeve. BioSleeve, on the other hand, was associated with multiple follow-up periods, and each one was recorded against the age of the patient at the time of follow-up and the total period length. The model accounts for the impact of age, length of treatment period, gender, diagnosis and arm usage. The final model, identified by stepwise regression, included only the method of treatment as the best-fitting model to explain arm usage. The model showed a highly significant correlation (p value < 0.0001) for the method of treatment irrespective of the other factors modeled. Accordingly, the period of treatment, patient age, gender, and diagnosis were secondary to the method of treatment to explain arm usage.

A second stepwise generalized linear model of arm usage considering the period of BioSleeve use against patient age, gender, period of treatment, usage hours per day, and diagnosis identified the period of treatment and hours of usage per day as the main factors in the final model. Interestingly, the usage hours per day was not a significant factor; however, the cohort of patients did not show a wide variation
in the time used per day. This indicates that the period of treatment is the main significant factor in determining the final arm usage of the patients using the BioSleeve.

**Arm Usage Significantly Increases Progressively with BioSleeve Intervention**

Patients were tracked for up to a period of 10 years post-BioSleeve intervention. A third generalized linear mixed-effects regression was used to model the progressive change in percentage of arm usage across follow-ups against the fixed effect of disease onset age, age of patient at the start of BioSleeve usage, arm usage before the BioSleeve, and patient diagnosis. In addition, the number of years of BioSleeve usage was modeled as a random effect for every patient. The random effect accounts for variations in patient response themselves and variations between patients. Stepwise regression was used to select the best model. The final model showed a significant positive correlation with the number of years that the patient wore the BioSleeve, with an average increase of 5.31% in arm usage every year (p<0.0001). The model showed, however, that TBI patients are the cohort of patients showing the most remarkable changes, TBI patients showed a high average prior arm usage of 23.6%, which progressively increased over the years, and a posttreatment arm usage of 88.3% at the last follow-up. The linear mixed-effects model of the TBI patients showed a significant relationship between years since fitting and arm usage (p<0.001), with an average effect of 5.67% per year (Figure 8).

While a similar trend was observed in the CVA patients (Supplementary Figure 7), the cerebral palsy (Supplementary Figure 8) and hemispherectomy cohorts (Supplementary Figure 9) did not show similar effects, although those groups comprised smaller sample sizes. Interestingly, some patients in the non-TBI cohorts showed a decline in arm usage function (Supplementary Figure 6). As shown in Figure 6, a decrease in the percentage of arm usage is primarily due to the contribution of a few patients who either stabilized or reported less arm usage in the year 9 follow-up. The year 10 follow-up showed improvement, perhaps biased by improvements associated with both patients who adhered to follow-ups. The mixed-effects model considered both the cohort and patient effects.

**Study Limitations:**

Retrospective cohort studies such as ours have known limitations. First, the study may be subject to recall and recency bias (wherein patients are likely to overrepresent recent observations over longer trends); however, the reported arm usage improvement is more significant than a random variation in arm usage over time, as shown in the longitudinal statistical models. Second, the data were not systematically randomly sampled, but we relied on random patient walking into the clinic. Additionally,
the TBI group is overrepresented, as they were able to benefit from medical insurance to obtain the device. Hence, we tested the TBI group independently from the other groups. Third, the potential for biased reporting exists, i.e., patients may feel compelled to report improved outcomes. To control for this experimenter bias, patients were not given an incentive to report improvements – they were not paid to participate in the study, no additional therapy was provided, and no increase in medical benefits resulted from participation in the study. Fourth, our study did not have a control group to compare; however, in the analysis, we relied on case crossover methodology, wherein patient response was compared pre- and postintervention. Fifth, our study is semiquantitative, as individual perceptions may interpret arm usage differently; for example, a 60% arm usage for one patient may not mean the same for another patient. This would have affected the stability of the reported arm usage; however, we found less variability than the significant variability of the improvements. Sixth, follow-up visits were not consistent between patients, and some complied better than others; therefore, some patients were followed over a longer period than others. However, we treated all patients as one cohort with expected dropout percentages, all baselined to the same start. Seventh, although reporting clinical outcomes is a first critical step in the discovery of medical knowledge and is sometimes the impetus for future research, this retrospective study was the culmination of work done by Axiobionics, which has commercialized the BioSleeve device. To overcome inherent bias, the data collected were reviewed by an independent expert in medical statistics who performed all mathematical computations. Future studies will be conducted in conjunction with one or more independent institutions, randomized and controlled.

**Discussion**

Impaired primary motor cortex (M1) cortical function results in a reduction or absence of contralateral limb mobility. The rehabilitation of arm mobility after brain insults and infarcts remains a necessary therapeutic goal (64). Current therapeutic interventions include neurorehabilitation via in- and outpatient therapy (64, 65), noninvasive cortical activation (such as transcranial magnetic stimulation (66, 67), and subcutaneous and transcutaneous electrical stimulation (67–69). However, there remains vast inconsistency in the literature with respect to technological intervention, individual experimental parameters, sampling and, consequently, results (70). NMES is one type of ES wherein affected limbs can be activated by stimulation with an array of cutaneous electrodes. Previous work has shown promise for the usage of NMES in rehabilitation settings such as urinary retention (71), dysphagia (72) and ataxia (73). However, there remains a scarcity of evidence tracking long-term interventional NMES effects on arm usage. Herein, we tested the use of the Axiobionics BioSleeve NMES device in a retrospective study consisting of patients with hemiplegia or hemiparesis.

In our study, hemiparetic and hemiplegic patients (n = 38) were fitted with an NMES device (BioSleeve). The current retrospective study followed patients up to 10 years, recording their reported arm usage during the follow-up visits. To our knowledge, this makes our study the longest retrospective analysis examining the effects of electrical stimulation of muscle as a rehabilitation therapy. Initially, we compared the patient’s conventional therapy with the NMES therapy, as each patient received some therapy since disease onset. The conventional therapy outcome was determined to be baseline reported
arm usage prior to the BioSleeve fitting. The current cohort studied had a majority of TBI (n = 23) patients, followed by CP (n = 7), CVA (n = 4), and hemispherectomy (n = 4). This disparity in sample size was due to a logistical limitation. Currently, NMES devices are not easily approved for insurance coverage, except in cases of insurance payouts from automobile accidents resulting in TBIs. On the other hand, cerebral palsy (CP), stroke, or hemispherectomy patients paid out of pocket and were therefore less likely to purchase the NMES device. Hence, we see the highest power in our TBI patients; however, we did not exclude the results of other diagnoses, as it offered the ability to test the generality of the method of treatment across all four diagnoses.

We used a mixed-effects model to test the general impact across all diagnoses. The model assumed a case crossover, where the same case undergoes conventional therapy and subsequently participates in NMES therapy. The model showed that NMES therapy provided significant improvement over conventional therapy when accounting for diagnosis, the age of the patient, length of treatment, and gender. The model showed that the method of treatment (conventional vs. NMES) was the main distinguishing factor of improvement in arm usage. We utilized a stepwise regression method as an iterative mechanism for our model. Stepwise regression is the recommended statistical approach to identify the optimal combination of variables that best fit the data, given the assumption that the variables are independent.

We observed an improvement in arm usage irrespective of diagnosis; however, we observed the largest improvement in TBI, with an average increase of 48.8% ± 27.7%. Our other cohorts showed smaller improvements in arm usage, CVA followed by CP, and hemispherectomy (see Fig. 6). A total of 21/23 of our TBI patients exhibited an increase in self-reported arm usage, demonstrating evidence for the suitability of the BioSleeve for facilitating arm recovery in this type of patient. Our results support existing work that has established cutaneous or transcutaneous electrical stimulation to reverse the loss of arm movement (70, 74–76). Our study shows that there is potential for long-term improvements in arm usage across hemiparetic patients. Unlike other studies, the usage of the BioSleeve facilitates the ability to stimulate the affected arm without discomfort and in the home environment.

The disproportionate increase in motor recovery in TBI patients compared to other diseases is potentially biased by a significant disparity in sample sizes in our cohort. Interestingly, a recent study examining potential improvements in arm usage after cutaneous electrical intervention also observed a greater improvement in their TBI groups (n = 8) over their stroke group (n = 8), although their result was not statistically significant (74). If there is indeed a robust difference in rehabilitation related to disease states, this may be due to the neurobiology and neuropathology of the disease states themselves. Recovery has been reported to include the activation of the premotor cortex (77) and other motor pathways (78–80). Yeo and Jang (2012) reported that arm recovery can occur via activation of the ipsilesional motor cortex after an MCA infarct (80). The interrelationship between infarct severity and penumbra recovery results in significant heterogeneity in the presentation of stroke-related motor deficits. This is in line with established knowledge that the risk for stroke onset increases significantly with age (81). Consistent with the results of that study, our stroke cohort was older than our other cohorts. Another
source of heterogeneity is the severity of the initial motor deficit, as it has been previously reported that individuals experiencing mild to moderate poststroke arm paresis show larger improvement outcomes than individuals with severe paresis (82–85). Our study tracked a small population of stroke patients with a range of arm mobilities at the time of intervention.

We postulate that the combination of the relatively young age of the cohort and the potential for focal TBI may enable an increased chance of recovery in comparison to other groups. Our TBI group was younger than the stroke group. It is posited that the potential for angiogenesis (86, 87), neuroplasticity (88, 89), and rewiring of brain regions decreases as a function of increasing age, potentially due to an age-dependent loss of neural progenitor cells (86). Conversely, other studies have shown that muscle re-education and recovery do occur, even in elderly patients in response to activity (90–92). Therefore, it is possible that the disproportionately large improvement in our TBI cohort, relative to our stroke cohort, may be a result of an underpowered stroke cohort and/or the relatively young age of the TBI cohort. Concomitantly, hemiparesis associated with TBI can be due to a heterogeneity of affected brain regions but likely includes the motor cortex. Without knowledge of the severity of TBI – data unavailable to us – we were unable to factor TBI severity as an additional variable to consider in terms of motor recovery. It is plausible, however, that there was a self-selection bias among the TBI group – only those individuals who experienced moderate TBI and maintained some arm mobility were likely to use the BioSleeve. Individuals suffering from mild TBI (e.g., sports-related concussions) often do not experience motor abnormalities and are less likely to participate in such a study. Concomitantly, individuals who experienced a severe TBI – potentially resulting in severe sequelae – may not consider arm usage recovery to be a therapeutic priority. Future work with the BioSleeve should examine whether improvements in motor function are inversely correlated with disease severity.

A key finding from our study was that incremental improvements were not related to the age of the patient, gender, hours of device usage per day, or disease onset age. The main factor affecting the progress of arm usage rehabilitation was the total number of years that this device was used. Conversely, some patients in each group showed either no improvements or a decline in arm usage. The potential reasons for limited responses are multifactorial but include heterogeneity in disease severity, inconsistent or incorrect usage of the device, differences in usage time or settings, differences in age and errors in patient reporting. Additionally, early BioSleeve intervention may be more beneficial than late intervention due to better management of muscle weakness and atrophy.

We observed significant heterogeneity within disease groups. Specifically, 3 out of 4 patients in the stroke group showed marginal (10%) improvements, while the final patient (#25) showed a 55% improvement in arm usage. While patient 25 (Supplementary Fig. 6) had the highest time of intervention out of the group, this is likely not the only reason for this disparity in improvement, as patient 27 had a similar intervention length but showed a marginal improvement. In the TBI group, we observed the best response to the BioSleeve intervention, although there were two individuals in our TBI cohort who did not show any improvements. These individuals (Patients 19 and 23) had a self-reported score of 0 arm usage both before and after the BioSleeve intervention. On the other hand, other patients in the TBI group (#3, #31
and #36) reported increased arm usage despite starting at a score of 0. Therefore, even within our TBI cohort, there remains some heterogeneity in response. Future work should explore this disparity in response and may elucidate new avenues for personalized medicine.

The wearable BioSleeve device increased arm usage compared to conventional therapy alone, as shown in the first model that showed the method of treatment as the main significant effector for patients across the 10 years of follow-up before and after the BioSleeve device was fitted. The second result also showed that the device showed a significant linear improvement in patients with time.

While our retrospective longitudinal design does not allow for an understanding of causation for improvements in upper arm mobility related to NMES, other work has posited a variety of potential mechanisms. These mechanisms range from a direct, short-term effect, such as impaired motor protein or ion channel expression (93, 94), to a long-term indirect effect, such as a potential long-term potentiation (LTP)-like mechanism involving rewiring and strengthening of synaptic connectivity (14, 95–97). Veldman et al. (2014) have speculated that this LTP-like pathway begins via activation of the sensory neurons emerging from the NMES-activated muscle, projecting axons to the dorsal root ganglion in the spinal cord. Subsequently, activation of the sensory dorsal medial lemniscus pathway is followed by the decussation of spino-cortical projections and the activation of contralateral S1 sensory cortices via intermediate thalamic projections (14). Consequently, projections between S1 and M1 are hypothesized to potentiate the M1 motor cortex (14, 98, 99). This innervation and potentiation of the affected and unaffected M1 cortices is an exciting potential focus for future work but remains speculative for now. More research is needed to determine the mechanism underpinning the BioSleeve-mediated increase in arm usage.

**Conclusion**

To our knowledge, this is the first research study showing improvement in arm function in hemispherectomy patients. Intractable seizures that do not respond to pharmaceutical management (100) can respond to surgical intervention by eliminating epileptogenic tissue (101), particularly in pediatric patients (10). The temporal cortex is a region associated with a comparatively high risk of seizure origin (102). Due to its proximity to the parietal lobe and the difficulty of performing these surgeries on developing brains, excision of tissue from the temporal lobe can result in hemiparesis, potentially due to loss of motor cortex gray matter and/or associated white matter tracts (103-105). This results in the loss of upper motor neuron function due to the loss of somatosensory neural tissue. For reasons not entirely understood, postsurgical motor sequelae of hemispherectomy negatively affect upper limb function more than lower limb function (106). The usage of the BioSleeve significantly increased arm movement in a subset of our patients, although the variance in response was high, with 1 out of 4 patients not showing any improvement in arm usage. Similarly, we observed a statistically nonsignificant increase in arm usage in our CP patients. The inconsistency of outcomes in these two cohorts may be related to a low sample size, the inconsistency of hemispherectomy surgeries,
and the difficulty of ascertaining improvement in a pediatric population due to an additional layer of observer bias introduced by parental reporting.

In summary, we report a novel wearable and commercially available device, the BioSleeve, that increases arm mobility after cortical insult, infarction, or excision. The study revealed the most robust results in a sample of TBI patients. The device was well tolerated for usage across a wide age range (1.8-73 years) and has the potential for long-term, at-home usage. Future studies should compare the usage of the device in affected individuals utilizing a prospective cohort design.

Future Considerations:

In this study, we present the potential benefits associated with the application of a wearable neuromuscular rehabilitation system suitable for long-term (ambulatory) use. It is critical that further efforts be made to develop cost-efficient, comfortable, and effective wearable rehabilitative systems that provide intervention outside the walls of a traditional health care system.

Wearable NMES solutions offer a cost-effective and practical method for individuals to help re-educate motor function, improve limb mobility, reduce muscle atrophy, improve joint range of motion, and enhance local blood flow to maximize patient potential.

Individuals who suffer from hemiplegia require access to better long-term assistive and rehabilitative approaches. Emerging research and converging technologies support the future use of neuromodulation techniques and neuroprosthetics, including wearable systems. Future solutions will be adaptive, guided by central nervous system interfaces and external sensors coupled with predictive artificial intelligence.

Abbreviations

ADL
Activities of Daily Living
BIC
Bayesian Information Criterion
CNS
Central Nervous System
CP
Cerebral Palsy
CVA
Cerebrovascular Accident
ES
Electrical Stimulation
Declarations

Ethics Approval: The progress of patient arm usage was the main outcome of this study. IRB Protocol #21-AXIO-102. Human Subjects Research: This study was determined by the Institutional Review Board to be Exempt according to FDA 21 CFR 56.104 and 45CFR46.104(b)(4): (4) Secondary Research Uses of Data or Specimens on 10/01/2021. IRB review was provided by Gretchen Parker, PhD, RAC, CIP IRB Chair, Pearl IRB 29 East McCarty Street, Suite 100 Indianapolis, IN 46225.

Consent for Publication: Consent was provided by the participant shown in Figure 5.

Availability of Data and Materials: All data will be published and available as supplementary information.

Competing Interests: PM is the founder and CEO of Axiobionics, LLC. JS is an employed clinician at Axiobionics, LLC.

Funding: All work was funded by Axiobionics, LLC.

Authors’ Contributions: PM served as the primary clinician in the study and collected all data. RS performed the statistical and qualitative data analysis. DD, ED and NC provided guidance on adherence.
to clinical standards. JS was involved in data collection efforts. All authors were involved in the writing and editing of the manuscript.

Acknowledgements: None.

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### Tables

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*Table 1: The current cohort of patients was tested for differences between diagnosis, disease onset age, gender, and number of therapy years - either conventional or BioSleeve. This was to identify if there were statistically significant differences between the groups along with the statistical power of the tests. There were significant differences in age of disease onset, BioSleeve age, and conventional therapy years across diagnoses. The cohort does not show significant differences in gender or BioSleeve years. See Supplementary Figures 1-5.*
<table>
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<td>7.5 ± 0.44 (5.0-10)</td>
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<td>Average and Range of Arm Usage After Wearing the BioSleeve (%) (M±SE)</td>
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<td>33.0 ± 3.4 (0.0-60.0)</td>
<td>25.0 ± 2.7 (15.0-50.0)</td>
<td>36.2 ± 4.3 (5.0-70.0)</td>
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<td>Average and range of change in arm usage after BioSleeve - before BioSleeve (%) (M±SE)</td>
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<td>Average Time the BioSleeve was worn in one day in Hours (M±SE)</td>
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**Table 2:** Overall, 35/38 patients reported improvement in arm usage in response to BioSleeve intervention. The magnitude of arm improvements varied across the four cohorts. The largest improvement in arm usage was reported in the TBI group.

## Figures

### Figure 1

See above image for figure legend.

### Figure 2

See above image for figure legend.
Figure 3
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Figure 4
See above image for figure legend.

Figure 5
See above image for figure legend.

Figure 6
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Figure 7
See above image for figure legend.

**Figure 8**

See above image for figure legend.

**Supplementary Files**

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