Botulinum toxin for writer`s cramp patients: A study with multi-channel EMG

Venkateshwarla Rama Raju

Professor, Dept. of CSE & Neurology, CMR College of Engineering & Technology, Hyderabad, India
Nizam`s Institute of Medical Sciences, Hyderabad, India

***Corresponding Author: Venkateshwarla Rama Raju**
Email: drvenkateshwararrr@gmail.com

Abstract

Injection with Botulinum toxin in the dystonic muscles of writer's cramp is the most effective therapeutic treatment (method) available today for the other movement disorders such as dystonia. Botulinum toxin is a protein produced by the bacterium Clostridium botulinum. It is the most toxic protein known with an LD50 of roughly 0.005-0.05 µg/kg. It was noted in 1950s that injecting overactive muscles with minute quantities of botulinum toxin type-A would cause a decreased muscle activity by blocking the release of acetylcholine at the neuromuscular junction, thereby rendering the muscle unable to contract for a period of 3 to 4 months. 12 Writer`s cramp patients included in this study and their prognostic analysis are experimentally diagnosed and the analysis are given under.

Twelve patients with writer's cramp (8 with concordant and 4 with discordant MMs) were assessed. On comparison of the measures of dispersion; D group had statistically significant difference between LHWS and RHWS (variance, standard deviation and F ratio) with a larger variance in RHWS, as compared to C group where variances and SD were equal or smaller in the RHWS compared to LHWS. Mean amplitudes for RHWS and LHWS for the same muscles, though differ significantly in statistical terms, showed a consistent pattern only in the fifth muscle with a larger mean amplitude on left side in all patients and were not of value in differentiating between concordant (C) and discordant (D) groups of patients. The principal component (PC) scores of the 12 patients showed 80% variance in our computation in the scatter plot diagram. The cluster analysis based on dissimilarity among the patients' signals show a possibility that, in addition to the grouping of patients as C or D, some other groupings may also be meaningful. EMG-EMG coherence was assessed in the Writer's cramp hand muscles, namely ECR, ECU, FCR, FCU, followed by 5th muscle. The coherence computed, evaluated and compared between flexor aspect of forearm and extensor aspect of intrinsic hand muscles was showed significant coherence in both groups. These observations suggest that the nature of EMG-EMG coherence in dystonia writer's cramp may be constrained by the descending motor systems, both in terms of their anatomical distribution and their frequency characteristics. This study showed significant quantifiable EMG differences in the signals seen while writing with the right and left hands between those writer's cramp patients with concordant mirror movements (C group) versus those with discordant mirror movements (D group). This was mainly seen in the measures of dispersion of the signal i.e., standard dispersion, variances and their ratio (F-ratio). These were statistically significantly different between the two groups, C and D, and the pattern of differences were consistent with the hypothesis that the discordant group had a compensatory force which overcame the dystonic force resulting in the final abnormal posture. This was seen in the form of larger variances and standard differences in the RHWS in the D group as compared to the C group, as the dystonic and compensatory forces both contribute to the instability. These differences were robust and seen in every measure of dispersion, such as in the patterns of significance of f-values for ratios of variances. Cluster analysis and more sophisticated analyses using advanced multivariate techniques leading to effective data summarization and measures of dissimiliarity between patients as reflected in the signals recorded and consequent possible clustering among them, however, did not lead to any meaningful clinical conclusions. These analyses could possibly be applied to longitudinal follow-ups and correlations with a normal control population in future to better comprehend the phenomenon of Writer's cramp.

Keywords: ECR, ECU, FCR, FCU.

Introduction

Botulinum toxin is a protein produced by the bacterium Clostridium botulinum. It is the most toxic protein known.[1-3] with an LD50 of roughly 0.005-0.05 µg/kg. It was noted in 1950s that injecting overactive muscles with minute quantities of botulinum toxin type-A would cause a decreased muscle activity by blocking the release of acetylcholine at the neuromuscular junction, thereby rendering the muscle unable to contract for a period of 3 to 4 months.

Alan Scott,[4] a San Francisco ophthalmologist, first applied tiny doses of the toxin as a medicine to treat squint and a focal dystonia of the eye –blepharospasm. Since then botulinum toxin injections have been used in various disorders including dystonia and writer's cramp. There are seven serologically distinct toxin types, designated A through G; 3 subtypes of A have been described. The toxin is a two-chain polypeptide with a 100-kDa heavy chain joined by a disulfide bond to a 50-kDa light chain.[4]

Type A, B and F, have been used for medical purposes and are currently marketed. Mechanism of action: Following the attachment of the toxin heavy chain to proteins on the surface of axon terminals, the light chain is taken into the cell by endocytosis and is able to cleave endocytotic vesicles and reach the cytoplasm. This light chain is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction. These fusion proteins are required for anchoring the acetylcholine vesicles at the neuromuscular junction. By inhibiting acetylcholine release, the toxin interferes with transmission of nerve impulses to the muscles and causes paralysis of muscles.

Botulinum toxin (BoNT)/Botox in writer's cramp

The use of BoNT to treat limb dystonia requires thoughtful technique including customization of doses and muscle selection.

American Academy of Neurology (AAN) recently reviewed the various trials proving the efficacy of BoNT for focal limb dystonia.[5] A large trial conducted by Kruisdijk JJ et.al.[6] randomized 40 patients (class I) with writer's cramp in a double-blind design to BoNT or an equivalent volume of saline placebo. Injected muscles were chosen based on clinical examination. Participants with inadequate or no response were offered a second injection 1 month later. The primary outcome measure was the subject's stated desire to continue injection. Seventy percent of those randomized to BoNT wished to continue treatment compared to 32% of those receiving placebo (p=0.03). Significant improvement was also found in BoNT-injected subjects compared to those receiving placebo in secondary outcome measures including a visual analog scale, symptoms severity scale, writer's cramp rating scale, and assessment of writing speed, but not in the functional status scale. Temporary weakness and pain at the injection site were the only adverse events reported.[6,7]

Similar results of various smaller placebo controlled trials evaluating the efficacy of BoNT in writer's cramp (Class II trial) are given below in the table.[8-10] Injection with botulinum toxin in the duystonic muscles of writer's cramp is the most effective treatment available today.[2]

Materials and Methods

Patients, materials and methods

Patients

12 consecutive patients (M: F =11:1) diagnosed to have writer's cramp were included in the study done from March 2000 to 2003. All patients were right handed individuals

All patients were informed about the study and written informed consent was obtained from them. Detailed clinical history using a standardized questionnaire was taken from all. The clinical details of the 12 patients are given in table 5.

Videorecording during assessment of dystonia and mirror movements were done after consent for later perusal. All patients were initially asked to write with their right (dominant) hand for 4 minutes and then with left (non-dominant) hand for another 3 to 4 minutes using a standardized protocol. During the latter phase, they were asked to maintain the right-hand flexed on the elbow in a semi pronated position and the wrist in a neutral position, with fingers being kept relaxed in a semi-flexed position. The right hand was observed for mirror movements (MMs) while writing with their left hand. Writer's cramp severity was graded according to the writer's cramp rating scale by a neurophysician.[1,10] Videotaping was done serially from two angles during the procedure.

EMG recording

Sterile nylon coated innocuous fine wire electrodes were introduced into five muscles for a detailed and muscle specific EMG recording. As most discordant muscle movements are those of wrist, 4 muscles causing flexion and extension of wrist viz, ECR, ECU, FCR, FCU were analyzed in all patients and one more muscle (as decided by the Neurologist, for example, ADP, APL, etc. which showed the maximum discordance of mirror dystonia) on the right hand was included. The fifth muscle selected for each patient is given in Table 1. EMG signals were simultaneously recorded from all five muscles while the patients wrote with their right hand (Right hand writing signal – RHWS) and then with their left hand (left hand writing signal – LHWS

Microelectrodes

A set of five miniature microelectrodes each 50 micron, from California Fine Wire Company, USA, were used in each patient. Since the electrodes are inserted into specific target muscles, unlike in the case of surface EMG, flexor electrode amplifiers contributed only to flexor contraction muscles (i.e., FCR, FCU, during writing during mirror movements), extensor electrode amplifiers contributed only to extensor contraction muscles (i.e., ECR, FCR, during writing and during mirror movements) and 5th electrode amplifier contributed only to 5th muscle contraction (i.e., ADP/APB, etc) during writing and during mirror movements.

Table 1: Patient characteristics and clinical details

Writer's cramp *							
Case No	**Age (Year)**	**Sex**	**Occupation**	**Handedness**	**Duration (yrs.)**	**Date of Recording**	**5th Muscle**
A1	41	Male	Teacher	Right	12	16/02/02	APL
A2	61	Male	Veterinary Doctor	Right	5	08/02/02	EDC
A3	43	Male	Bus Conductor	Right	3	15/06/02	EPL
A4	30	Male	Bank employee	Right	6	29/01/00	FPL
A5	15	Male	10th class Student	Right	2	03/01/02	EPL
A6	42	Male	Excise controller	Right	1.6	11/05/02	FPL
A7	55	Male	Quality controller	Right	40	03/09/02	EIP
A8	39	Male	Doctor	Right	5	10/08/02	EIP
A9	16	Male	10th class student	Right	5	15/06/02	FPL
A10	41	Male	Bank manager	Right	2.5	19/06/02	EPL
A11	39	Female	Solicito	Right	10	03/05/02	APB
A12	41	Male	Clerk	Right	12	18/06/02	EPL

Motor control system

The motor control system is a complex neural system with a myriad of pathways. One of its output pathways consists of the ensemble of α-motoneurons which activates the skeletal muscle-fibers. One way to study this output pathway in humans is to record the 'motor unit potentials' ("if a sufficiently strong stimulus, e.g., if an electric shock is applied to whatsoever to the part of a nerve or muscle fiber, it will give rise to an excitation, the main manifestation of which there is a great rapid varied variation of the membrane potential (due to change in the ion permeability of the membranes), which is known as the action-potential' can be registered by two methods: by means of electrodes applied to the outer surface of an extra-cellular fiber, and by means of a microelectrode introduced into the protoplasm—intracellular associated with firings of individual motor units (MU's) or motor neurons by means of indwelling ('needle' or 'wire') electrodes placed in a target and/or specific muscle.

Results and Discussion

In this study of Writer's cramp, the investigation and the diagnostic value for clinical use together with the results obtained are explained below.

12 patients (M:F: 11:1) with Writer's cramp with mean age 38.5 ± 3 years and disease duration 104 ± 126.3 months were studied. They were initially asked to write with their right (dominant) hand for 4 minutes and then with left (non-dominant) hand for another 3 to 4 minutes. During the latter phase, they were asked to maintain the right-hand resting on the table flexed on the elbow in a semi pronated position and the wrist in a neutral position, with fingers being kept relaxed in a semi-flexed position. The right hand was observed for mirror movements (MMs) while writing with their left hand.

The right hand was scored according to the Writer's Cramp Rating Scale[68,90] for the position of the wrist, thumb, index and middle fingers – both while writing with the right hand (right hand writing signal – RHWS) and also while writing with the left (left hand writing signal – LHWS) [for right hand mirror movements (MMs)]. Videotaping was done serially from two angles during the procedure. Depending on the wrist position during writing with the right hand and left hand, the MMs were scored as concordant (C) or discordant (D) if the wrist posture were in the same or different directions respectively. It was seen that patients A1, A7, A11, and A12 fall in the category of 'Discordant' (D) group whereas the other 8 patients were 'Concordant' (C). (for MMs at the wrist).

Following this, a set of five innocuous fine micro wire electrodes were inserted into the right hand ECR, ECU, FCR, FCU followed by 5th muscle, which showed dystonic MM's. The patient was then asked to write once again with the dominant right hand and then with the non-dominant left hand and EMG signals recorded parallelly in Pentium computer (Fig. 1,2).

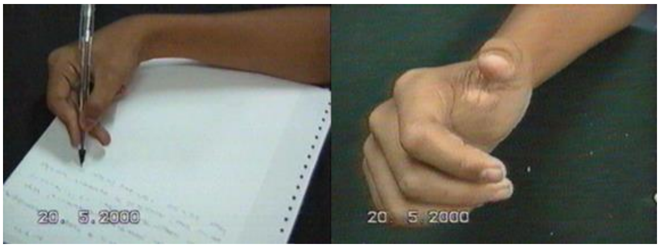

Fig. 1: Wrist flexor dystonia (right) with concordant flexor mirror dystonia (MD) in an 16 year old male. Note the discordant extensor thumb MD.

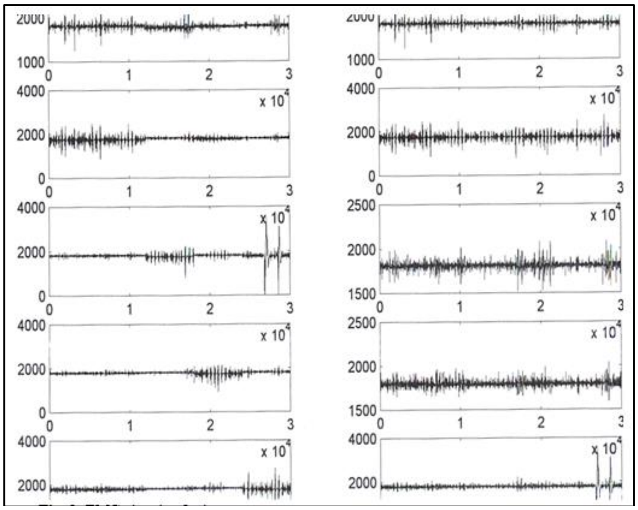

Fig. 2: EMG signals of mirror movements

Mirror movements (MMs) are seen in the right hand in Writer`s Cramp (WC) patients when writing with the left hand. These MMs can be similar to the original dystonic movement while writing with the right hand (concordant) or in the opposite direction (discordant). The aim of present experimental investigation is to attempt to differentiate between those with concordant (C) and discordant (D) MMs in WC, in order to establish that there is a quantifiable difference between these two groups and to design and fabricate a multi-channel EMG system. This study was conducted at Nizam's Institute of Medical Sciences a tertiary care centre. Study period was from August 1997 till 2003. A suitable multi-channel EMG system was designed and fabricated to record digitized EMG signals simultaneously with a set of five, intramuscular, nylon coated fine wire electrodes (50 micron diameter).

The basic signal data consisted of EMG-data gathered from 5 muscles of the right hand, when the patient wrote first with right hand and then, wrote with his/her left hand i.e., right hand writing signal (RHWS) and left hand writing signal (LHWS). Duration of signal recording was 10 seconds, with 3 KHz sampling frequency, giving 30,000 readings for each muscle. Means analysis, differences in means, standard deviations, variances, t, F and p-values between RHWS and LHWS were compared using student *t*, χ^2 (*Chi-square*) and Fisher's tests. Advanced statistical methods/ techniques employed in the present study include singular value decomposition (SVD)/ Eigen analysis, principal component analysis (PCA), Distance function, simple and (hierarchical) clustering, Canonical correlation/multidimensional scaling and EMG Coherence.

Conclusion

This study showed significant quantifiable EMG differences in the signals seen while writing with the right and left hands between those writer's cramp patients with concordant mirror movements (C group) versus those with discordant mirror movements (D group). This was mainly seen in the measures of dispersion of the signal i.e., standard dispersion, variances and their ratio (F-ratio). These were statistically significantly different between the two groups, C and D, and the pattern of differences were consistent with the hypothesis that the discordant group had a compensatory force which overcame the dystonic force resulting in the final abnormal posture. This was seen in the form of larger variances and standard differences in the D group as compared to the C group, as the dystonic and compensatory forces appeared to contribute to the instability.

In the D group larger variances and standard deviations (s.d.) were seen in the right hand writing signal (RHWS) as compared to the left hand writing signal (LHWS). In the C group variances and standard deviations were equal or smaller in the RHWS compared to the LHWS. These differences were robust and seen in every measure of dispersion, such as in the patterns of significance of f-ratios of variances. The mean amplitudes for the RHWS and LHWS, which were recorded for the same muscles while writing with either hand, though different in statistical terms in each patient, did not throw much light on the differences between patients and were not helpful in differentiating between the C and D groups.

While the cluster analysis based on dissimilarity among the patient's signals showed a possibility that in addition to the groupings of patients as C or D, some other groupings may also be meaningful. The data analyses made in this direction showed some significant findings which led to attempts at more sophisticated analyses using advanced multivariate techniques leading to effective data summarization and measures of dissimilarity between patients as reflected in the signals recorded and consequent possible clustering among them. However, these did not lead to any meaningful clinical conclusions. These analyses could possibly be applied to longitudinal follow-ups and correlations with a normal control population in future to better comprehend the phenomenon of Writer's cramp. Injection with Botulinum toxin in the dystonic muscles of writer's cramp is the most effective therapy/ treatment available today for the other movement disorders such as dystonia.

Conflicts of Interest

All contributing authors declare no conflicts of interest.

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None.

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