BoTox in writer's cramp: A study with multiunit multichannel electromyographic EMG signal recording

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Abstract
B o Tox in type "A" group has become the treatment of choice for writer`s cramp (WC) for most types of focal dystonia. This study is to explore the effectiveness of BoTox in Type "A" group inoculations in subjects with WC in a double-blind, randomized, placebo-controlled trial, plus to estimate the follow-up the findings of outcome. 40 applicants were willingly randomized to medical management with either BoTox-"A" (Botulinum-Toxin) group or placebo injections in two sessions/stages. Experimental-investigation (period) was 12-weeks. The principal result degree-measure was the subjects' optimal-choice to resume with medical-management, despite its likely hindrances. Lesser consequence events comprised and incorporated some quantifiable-clinical rating scales on the levels of impairment and disability. The data was acquired with multi-channel multi-unit EMG system. The basic signal data consisted of EMG-data gathered from 5 muscles of the right hand, when the patient ascribed first with right hand and then with their left hand i.e., right handwriting signal (RHWS) and left hand writing signal (LHWS). Duration of signal recording was 10 seconds, with 3kHz sampling-frequency, yielding 30,000 readings for each muscle. Assessments were made at baseline plus 60days (second-result) and 3 months (first-result). Duration of follow-up was 365days. 39subjects accomplished the trial. 14 of 20 subjects (69.9%) receiving BoTox- Type "A" group stated a positive-upshot and indicated to resume action, against 6 of 19 subjects(32%) in the placebo-set which was statistically significant at 5%($p \leq 0.03$, Chi-square$\chi 2 \approx 4.2857$ for 1 degree-of-freedom). The variations on most of the irrefutable-experimental rating-scales were significantly in favor of BoTox-"A". Dyskinesias were faintness-in-hand (minor and momentary transient), and ache at the dose (inoculation) site. Following365days, 20of39 subjects were still in medication with a +Ve-result. Diagnosis with BoTox- Type Group "A" doses led to a higher-progression equated with placebo, as stated by patients' view medical valuation gages. Dimness in the hand is a dyskinesias of BoTox-Type Group "A" doses, then in spite of this cons, most subjects favored to resume medication.

Keywords: Chi-square, Mean-duration, Variance, Degree of freedom, Statistical significancy, Botulinum-toxin-type "A" (BoTox-"A"); functional-status-scale (fss);, severity-of-symptom-scale (sss); Visual-analogue-scale (vas); Writer's cramp rating-scale (wsrs), Multi-channel MEG recording, Left hand writing signals, Right hand writing signal, Fs-sampling frequency.

Introduction
Writer's cramp is one of the commonest focal dystonias and was described 200 years before primary torsion dystonia.[1] One of the earliest references dates back to 1713, when Ramazinni described it in his book De Morbis Artificum "An acquaintance of mine, a notary by profession, still living, used to spend his whole life continually engaged in writing, and he made a good deal of money from it; first he began to complain of intense fatigue in the whole arm, but no remedy could relieve this, and finally the whole right arm became completely paralyzed.[2-6] In order to offset this infirmity, he began to train himself to write with the left hand, but it was not very long before it too was attacked by the same malady."[7] Later it was described by Bell and Bruck in 1831 as scrivener's palsy. With the onset of the Victorian era at that time, London's commercial center created a large number of scriveners who were responsible for copying documents by hand using a quill firmly and some of them developed 'scrivener's palsy' which initially disabled writing and later affected other tasks.[8]However until 1930s it was considered to be a psychological disease, called as occupational neurosis by Gowers[9] It was only in the later in the twentieth century that a neurological basis was considered after Collier and Adi first suggested abnormalities of basal ganglia as the underlying pathophysiology[10] Even in the later half of the twentieth century many neurologists including Sir John Walton considered writer's cramp to be of psychogenic origin as described in the ninth edition of Brain's disease of the nervous system- "In my experience when even subtle physical signs are absent in the many 'simple' (Writer's cramp) cases that I have seen and neither other focal dystonia's nor any other organic disorders could in my view impair movements only when they take part in one coordinated act while leaving totally unaffected all other precise and complex voluntary actions involving the affected member".[11] Writer's cramps were first recognized to share common features with and was included in the group of focal dystonia's by Marsden and Sheehy. They also further classified writer's cramp into simple and dystonic writer's cramp[12] With the advent of various more sophisticated imaging signal modalities the organic nature of writer's cramp is no more in doubt. In connection with the treatment of writer's cramp, three randomized, double-blind, placebo-con- trolled studies have been undertaken, however, with small numbers of patients, different methods and inconclusive results.[13-25] We performed a randomized, double blind, placebo-con- trolled trial in 40subjects with WCs, to

evaluate whether the benefits of BoTox-"A" action dwarf its cons.

Materials and Methods

Experimental procedure

Patients were prospectively recruited from January 2001 to October 2003. They were eligible if they had signs and symptoms of idiopathic writer's cramp and had not benefited from BoTox-"A" before. The aim was to include as many BoTox-"A" native patients as possible. Patients were excluded if they were antenatal/or prenatal, and if they had multi-focal, generalized or secondary-dystonia, clotting/coagulation disorders or period-of-illness was365days. Subjects with marked-obviously writer's tremor were discarded. Wilson's disease was excluded for all patients by caeruloplasmin and copper blood tests. The study was performed on an out-patient-basis. Potentially suitable patients were referred by other doctors, recognized by the confined detective or self-referred as a result of publicity about the study. Patients were invited to attend for screening 2–4 weeks before the start of treatment. Diagnosis of writer's cramp was based on the typical clinical presentation, including observation of handwriting and classified as simple or complex writer's cramp.[1-13] Ethical clearance was approved and following Helsinki principles. All patients received written information and gave their informed consent. Patients were randomized to treatment with either BoTox-"A" injections or placebo injections. We allocated the patient a trial number and then forwarded relevant details to the central trial pharmacy. Randomization was accomplished by employing a computer program that allowed stratification according to the kind of writer's cramp simple or focal or dystonic.

Instrument calibration

Before each recording session, the signal was calibrated initially with a voltage of 2mV. After testing the calibration signals thoroughly, the apparatus was standardized which automatically measures calibration forever.

For every testing, the signals were viewed on an Oscilloscope; they were digitized on-line and the digital signals so generated were also displayed parallelly on the monitor screen of the computer. The values of the signal streams are stored on a hard disk, for further processing later.

Electrodes

For proper sterilization, half inch portion at both upper and lower ends, of the five innocuous micro wire electrodes (each 50 micron in diameter) was burnt with a spirit lamp and then packed (sealed) in a plastic-fiber folio. Later, they were sent for gas sterilization and kept for about 12 hours in GST lab. . A hypodermic needle with a bared tip and hub was used for positioning the wire into the muscle.

Muscle site selection with guided EMG

Each patient with Writer's cramp was seated comfortably in chair for sitting and writing. The electrode sites were found by palpating the muscle during a voluntary contraction and electrodes were inserted into specific-target muscles on identification of the traces on oscilloscope and based on the sound produced by oscilloscope and the neuro-physician expertise, accordingly. The skin was always cleaned thoroughly with spirit before the electrode placement. The placements were tested for accuracy, 'cross-talk', band connections, etc. by requesting the subject to perform several test movements (i.e., putting the particular muscle into action and detecting MUPs during minimal contraction) and test writing.

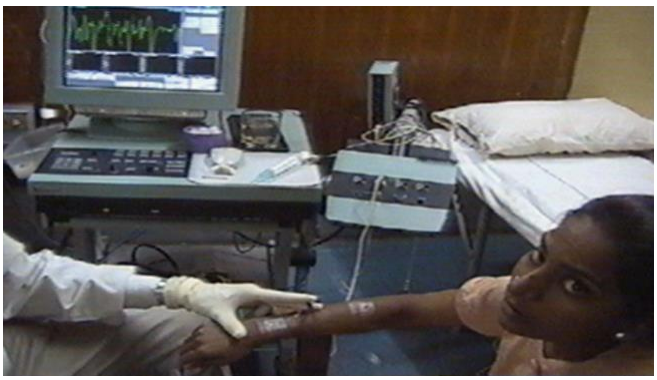

Fig. 1: Insertion of fine innocuous microwire electrode in Extensor Carpi Radialis (ECR) target muscle

If any malfunction was found, corrective action was taken and the test was repeated. (Fig. 1. In each patient, initially, muscle detection using these concentric needle micro-wire electrode recording was tested on Dantec's Key-Point Digital EMG machine (Fig. 1), a commercial one channel digital EMG equipment from Denmark, Europe).

EMG Signals Data Acquisition

After initial checking of the electrodes on Dantec Key-Point digital EMG machine, these electrodes were connected to the differential amplifiers of the 5 channel 'prototype' machine (figure 2) interfaced to the computer. The amplifiers have an input impedance of > 200 Mega Ohms and common mode rejection ratio of 58 dB. Each output channel was filtered to remove motion artifact and high-frequency noise using notch band pass filters with cut-off frequencies 0.5 Hz (Lower) and 10 kHz (Upper). A sampling frequency 3kz/channel was used (maximum sampling frequency provided to each channel was 6 kHz; maximum sampling frequency of the A/D card was 40 kHz/s). On-line signal recording was done with indigenously developed real time hardware and software. All the computation was performed using C/C++ and Mat_Lab utility tools processed on (IBM compatible) computer. In addition, for each channel the integrated EMG was formed.

Testing procedure

Each patient was asked to write initially with their right hand and then with their left hand using a standard paragraph dictated to them, while the EMG was recorded from all the five channels. Each test consisted of four randomized trials, each trial lasted for 10 seconds duration, with a rest period of

1 – 2 minutes between each trial. All five channels of EMG signals data were recorded digitized using a 12-bit A/D converter and processed on-line.

The target muscles under EMG monitoring of active movement and movement of the needle were also observed visually. A close of the signal recording can be viewed, depicted in figure 2.

Interventional study

Outstanding to separate transformations in dosage retort, subjects were diagnosed in two sittings: 1. The baseline assessment for 30days, 2. Following a month—if the subjects were pleased with the progress following the first session which is 30days. In that case no doses were administered at the second session. If patients had no response to the first doses, then it was doubled at the second session. In the case of inadequate retort or muscle-weakness, the dose and, if necessary, the site was adjusted following first session at the second session. This approach was preferred to optimize the treatment-result. Simultaneous treatment was unaffected throughout the trial. The Trial therapy comprised of BoTox-"A" or placebo doses. Freeze-dried BoTox- type "A" group was thinned (diluted-like-watery) to 20mouse-units per 0.1 milliliter of 0.9% sterilized briny-saline by an autonomous pharmacologist and enunciated in 1-milli syringes. Placebo boosts entailed of a comparable and equal-volume of 0.9% sterilized briny-saline. BoTox-"A" or briny-saline was boosted with guided multi-channel electromyography EMG signal recording into specific muscles using a deep-hollow, teflon-coated, 27 gauge-staggered and also bared needle. Actual muscles were preferred for boosting the drug according/bestowing and conferring to rendering to the pattern-signature of movements and perceptible or palpable and physical tangible hypertonia. The number of muscles boosted were varied consequently. The volume of fluid per boost-muscle-site was reliant on the sort of muscle. During initial appointment/visit, finger flexor muscles (FFM) were injected by 60IU-0.3 milli per capita fascicle, finger extensors with 10 to 15IU:0.05–0.075 milliliters per capita for every fascicle, wrist -flexors with 60 to 100IU (0.3–0.5 ml) and wrist extensors with 30 to 40IU:0.15–0.2milliliter.

Evaluation

All the subjects were evaluated before the medicational-treatment/(baseline), following the 4-weeks, 8-weeks and 12-weeks.

Subject's answers the main outcome for the queries like contemplating each pros and cons of this therapeutic-treatment, is the progression such that one wish to resume this medication? or not? this main outcome gauge was chosen because it takes into consequence not only the progression in dystonic-WC`s symptoms/ and syndromes just and the implications of hand difficulty for the diseased subject's regular activities plus more probable demerits/or cons of the medication. The first result outcome was evaluated during the twelfth week.

The next outcome gauges involved the following rating scales: 1.Visual-analogue-scale/vas26 for ascribing; 2. Severity-of-symptom-scale (sss)27;3-functional-status-scale(fss)27; 4.Writer`s Cramp rating scale:WCRS28; and finally5.ascribing speed.

Visual-analogue-scale is a self-measurement scale drawn by the subjects on a 10 cm line, on which zero (0) point to the most awful and potential position and 10 the best potential position. 26

Both the "fss" and "sss" were initially constructed for carpal-tunnel-disorder-CTS, were tailored to fit the particular problems of WCs. For this purpose, psychometrically evaluated the reliability of both multi-item scales in terms of homogeneity. The WCRS is an objective impairment scale and evaluates the dystonic movements or postures, their latency and duration, occurrence of writing tremor and writing speed. The ascribing velocity was quantified as the number of lines of a standard text written within 2minutes.

Statistical analysis

To detect the correctly applicable and also suitable size-of-samples, we based our computational-power on the hypothesis that BoTox-"A" therapy will yield a positive-outcome in 50% of subjects with WCs, and placebo therapy in 10% of WC-patients. With this hypothesis, 40 subjects enrolled and then recruited, 20 in every cluster, supplied 80% power-to-detect a meaningful disparity, i.e., variation at5% level (bilateral, i.e., right and left-sides).

The consistency and similarity, (i.e., homogeneity) or clinic-statistical logistic-coherence of the scale-items, of both "fss" and "sss" at the baseline plus eight-weeks follow-ups was stated in terms-of cron-bach's, a coefficient, and mean item-total correlational-coefficient. Standard electrical-baseline (i.e., zero line) characteristics of subjects were reviewed by employing the informative and descriptive-explanatory statistical-data. The resultant-size of the initial diagnostic-outcome was stated in terms of absolute-risk disparity (variance). The variation in percentages amongst the study-groups was evaluated by applying the chi-square statistic-test the $\chi 2$-statistic, and/or fisher's accurate-test if applicable. Also, we adjusted the initial resultant-outcome estimation for the electrical-baseline covariates, such as, gender, i.e., sex (male/female), age, duration/period-of-illness, type of WCs, by applying the multivariate logistic regression, i.e., size-of-effectiveness stated as OR-odds-ratio. Logistical-reasoning model was also applied to test for probable incidence of contact concerning therapy outcomes and type of WCs.

For secondary outcome, we computed, per-cluster, the change-of-mean in scores from electrical-baseline to follow-ups at eight-weeks. The mean change in scores of the patients receiving BoTox-"A" and those receiving the control drug were compared using the unpaired t test. Finally, the follow-up scores of the rating scales were analyzed by applying multiple linear regression, taking into account the zero-baseline values of is the concerning-scales, as well as subject's demographic characteristics such as, gender/sex, age, duration-of-illness(DOI) plus kind of WCs. Statistical uncertainty and biasedness was vented in 96% confidence limits(CL)/and degree-of-freedoms. Inferences were deduced

fitting to the intention to treat(ITT) basis and expected in accord with an investigational-study strategy granted by the tribunal operating commission before unblinding. The diagnostic findings were executed and staged by applying the s p s s software 11.5versioned.

Findings

The following Figure 2 shows the trial-flow/system-flow illustration.

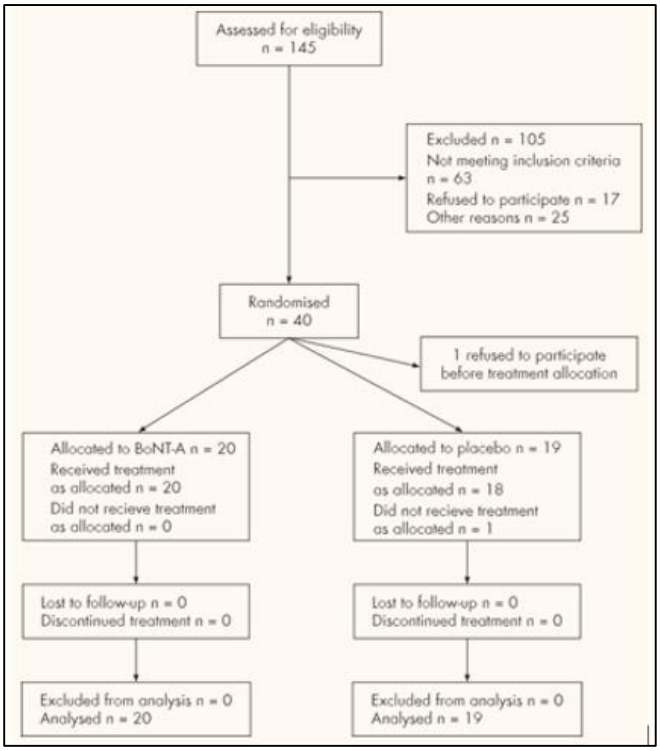

Fig 2. System-flow

Table 1 shows the baseline demographic and clinical characteristics according to assigned treatment. In general, patients' demographics were well matched, although some imbalance might be observed with regard to sex, disease duration and functional status. There were no patients lost to follow-up; all continued treatment and completed assessments until the end of the trial.

Table 1: Baseline demographic and clinical characteristics of the enrolled patients (n+39)

Varrible	**Placebo (SD)**	**Bo NT_A (SD)**
No of Patients	19	20
Women (no of patients)	7	10
Mean age (year)	45.63(7.90)	47.60(11.24)
Mean duration of illness(year) simple/complex (no of patients)	9.13(9.90)6/13	7.38(6.22)7/13
VAS handwriting	1.78 (1.39)	1.70 (1.20)
Symlom sevnity scale (joint)	27.32 (4.57)	28.10 (4.67)

Twenty-subjects were given BoTox-type-"A" therapy. The mean total dose of BoTox-type-"A"(Dysport) in these were 102-mouse-units ranging:30 to 220 at the first therapeutic-session and seventy-five at the post-session, i.e., second, ranging from:0 to 240. The total mean-dose for both were one hundred-seventy-eight mouse-units. The musculus flexor pollicis longus(FPL) was the most commonly injected muscle, followed by the musculus flexor digitorum (FDP/L) pro-fundus-ramus digiti2 followed by musculus-extensor indices-proprius(MEIP). Nineteen subjects were given placebo-therapy. The total mean-dose of placebo was equivalent in volume to eighty-two mouse-units ranging from 20 to 120 during first-therapeutic-dose-session, one-hundred-forty two during second stage ranging from 0 to 280. The total mean-dose for both-stages were two-hundred and twenty four mouse-units.

Outcome of diagnosis

In the BoTox-"A" group 14 of 20 WC subjects-70% longed to resume-therapy vs. 6 (6/19) WC-subjects31.6% in the placebo-group: absolute-risk-variation=38.4%; 95% C.L=(9.4%/67.4%), Fisher's exact-test: $p \leq 0.0349$, Chi-square$\chi 2 \approx 4.2857$ for 1 degree-of-freedom) in favor of the BoTox-type "A" cluster. Logistic regression, adjusting for the baseline covariates, also showed a substantial and significant treatment effect (OR = 9.9; 95% CL = 1.6/59.4, $p \leq 0.01$ which was statistically significant at 5% with a degree of freedom with a Chi-square$\chi 2 \approx 4.9271$). Six-subjects in the BoTox- type "A" disinclined to resume their medicine: one subject experienced no progress or dimness or paleness at all following two therapeutic-sessions; 2-subjects did have a good subjective and objective progression on ascribing yet not interested to resume the drug due-to feebleness. Finally, one patient had weakness without improvement.

Development follow-up

Following the randomized monitored-regulated-trial, all ninghteen subjects of the placebo arm were given BoTox-type "A" therapy. One WC subject had a positive effect on placebo refrained from BoTox-type "A". Another WC subject who has reacted to placebo had a restricted partial and limited rreply to BoTox-Type "A", however stopped the therapy due to his retirement. 3WC subjects who responded to placebo had a good response to BoTox-"A" and continued the treatment. Of the 13 patients who has not responded to placebo, 9-subjects with WCs had a positive response to BoTox- type "A". One subject who was given a BoTox-type "A" dose by gaffe or fault while at the second-therapeutic-session has not responded to initial-placebo-injection, however had a good-response to BoTox-type "A". In conclusion, 13 of 18 subjects (13/18, 72%) of the placebo arm, had a +Ve-outcome to the BoTox- type "A" group.

Conclusion

The wide-ranging behavioral retort in our study was meaningfully healthier in the BoTox-"A" cluster than in the placebo cluster, as presented by revealed by many subjective plus objective levels of dimension. Yet, not all consequence events mirror this progression. The fss exhibited no momentous change in the alteration scores amid the two behavioral arms which can be elucidated by a deterioration corrosion of some item scores due to BoTox-"A"-induced-feebleness, though the scores for the ascribing items progressed. A curb of fss is that it won`t differentiate the infirmity or susceptibility of dystonia from that of paresis. A delinquent in randomized, placebo-controlled examinations on the result of BoTox-"A" medication is the un blinding striking of the patient as an effect of paleness which is grim to deal with, as the BoTox-"A"-stimulated development in the dystonia is often supplemented by appetite. To deal this dilemma, the medication-effect was determined by using various objective-rating-scales. We found that the appetite was unconfined to the BoTox-"A" cluster. The results of open-label studies on the treatment of writer's cramp with BoTox-"A" have been encouraging, reporting favorable effects in 60% to 90% of diseased subjects i.e., WCs diseased subjects 29to31. However, comparison of these trials with each and every one may not be feasible at this juncture, since the evaluations and the choice standards applied in these trials were distinct.

Source of Funding

None.

Conflict of Interest

None.

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