ORIGINAL RESEARCH

Comparative Study of Botulinum Toxin 'A' on Upper and Lower Limb Spasticity: A Clinical Aspect

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Abstract

Aims and objectives: The study intended to compare the effect of botulinum toxin A on clinical aspects of spasticity recorded in various scales. It compared the data of upper and lower limb spasticity.

Materials and methods: This is an open-level prospective controlled study, involving patients with upper and lower limb spasticity. Assessment at 3, 12, and 24 weeks post-injections. The modified Ashworth, modified Tardieu scale of spasticity, percentage of passive range motion, Motricity Index for fine and gross motor activity were used. A total of 34 patients were enrolled—25 males, 9 females. There were 51 upper limb and 49 lower limb muscle groups. Three patients were lost after 3 weeks post-baseline follow-up.

Results: There was a significant improvement in all the parametric variables post-injections. Aggregate outcome scores comparing groups post-baseline showed a significant difference in modified Tardieu, Motricity Index, interventional goal assessment scales for lower limb muscle groups from upper limb.

Conclusion: It was concluded that botulinum toxin A has a definite effect on the impairment and focal disability within a rehabilitation setup of selected patients with focal spasticity.

Keywords: Botulinum toxin A, Modified Ashworth scale, Modified Tardieu scale, Range of motion, Spasticity.

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Introduction

Spasticity is derived from the Greek word *spasticus*, which means "to pull".

Spasticity is defined as a velocity-dependent (i.e., how fast the joint moves through its range) increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of stretch reflexes as one component of upper motor neuron syndrome. It is now accepted now that the exaggerated stretch of the muscle is only partly responsible for hypertonia and that other positive features of the upper motor syndrome such as co-contraction, athetosis, hyperreflexia, the release of primitive reflexes, dystonia, and biomechanical changes contribute significantly to the resistance to passive movement. Several neurological problems such as stroke, cerebral palsy, spinal cord injury, brain injury, multiple sclerosis, and other neurodegenerative disorder may cause spasticity.[1]

State-of-the-art botulinum toxins are an important weapon in the armamentarium. Seven antigenic forms of botulinum toxins are available A–G. Of this botulinum toxins A and B are used for therapeutic purposes. Botulinum toxin A cleaves SNAP-25. SNAP-25 is a protein, which docks neurotransmitter vesicles into the inner surface of the plasma membrane. This reversible chemodenervation prevents the release of acetylcholine from the nerve terminals.[2] The effects are reversed when preterminal neurons sprout and restore neuromuscular junction activity. Focal treatment with botulinum toxin helps to reduce the tone of injected muscles as well as break the disabling synergies. Local injections of botulinum toxin offer reversible, relatively painless, selective dose-related weakness by impairing the release of acetylcholine at per synaptic neuromuscular junction. These beneficial effects occur without sedation, dysesthesias, seizures, or hepatotoxicity. To maximize the outcome of botulinum toxin and other modalities are used in conjunction with each other.

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While the incidence of spasticity is unknown it is estimated to be around 12 million worldwide. In stroke, arm involvement is common up to 69% having weakness on admission to hospital. Sever upper limb hypertonia is a common complication of patients with stroke.[3] Only very few (approximately 5%) of these patients regain useful function of the paralyzed arm, and the prospect of recovery after the first 3 months is of stroke is negligible. When it affects distal lower limb such as ankle plantar flexors, eqinovarus foot position instance, reduced ambulatory speed, gait dysfunction and increased risk of falls may result. Lower limb spasticity may be a major cause of disability following brain injury.

The incidence of spasticity in spinal cord injury is approximately 70%. The incidence of cerebral palsy worldwide is 2/1,000 live births. In India, it is 1.5–2.5/1,000 live births. Spastic forms of cerebral palsy report about 70–75% of the cerebral palsy cases.

The cause of contracture and the relationship between this and therapy with botulinum toxin A must be examined. The principal cause of contracture appears to be the shortening of muscle fiber

length because of the reduced number of sarcomere precipitated by prolonged immobilization of the muscle at a short length.

The currently available conventional treatments are sometimes limited in the benefit they offer. Aspects of spasticity such as severity, topographical distribution, and effect on function determine which treatment strategy is most likely to confer maximal benefit. All treatment decisions should be made based on the goals of therapy. Treatment goals should be well established before treatment begins.

The recent licensing of botulinum toxin A for use in equinus deformity in cerebral palsy follows several years into benefits of weakening of spastic muscle in children.[4,5] Improvement using botulinum toxin A to treat the patient with traumatic brain injury with severe unresponsive spasticity of wrist and fingers were seen. Both range of motion and modified Ashworth in this patient without significant side effects.[6] Treatment with botulinum toxin A was proven to be valuable for counteracting spasticity in children with acquired brain injury it was noted that this treatment modality is not an appropriate treatment option for all children with severe upper extremity spasticity and appropriate muscle selection is needed care-full clinical assessment.[7] After stroke botulinum toxin A was found to reduce flexor tone in wrist finger and there was no adverse event associated with injection of botulinum toxin A.[8] Botulinum toxin A in treatment of spastic foot drop,[9] a condition causing significant interferences with stance and gait as a result of stroke or head trauma.

Aims and Objective of Study

- The effect of botulinum toxin A in the treatment of spasticity is due to various causes in the population
- To compare the effects of intervention in upper and lower limb spasticity.

Research Methodology

This study was an open level prospective controlled study, involving patients with spastic upper and lower limbs. No randomization, observer blinding or placebo treatment was undertaken. This study was conducted in the Department of Physical Medicine and Rehabilitation at the tertiary care institute of Eastern India. All patients were enrolled from September 2017 to February 2019. The follow-up period for all participants was at least 6 months. Inclusion criteria were the presence of moderate to severe spasticity for at least 3 months in focal joint muscle groups with a poor response to conventional physical and pharmacological treatment. The patient should have the ability to give informed consent and comply with given instructions on spasticity and motor ability measurement scales. Patients with spasticity ≥2 in Computed Modified Ashworth and Tardieu Scale were included in the study. An additional criterion was patients with functional difficulties. Patients excluded from the study were those with fixed contracture, profound muscular weakness, those who have received botulinum toxin or other chemoneurolytic procedures previously. Those who have received drugs or substances that affect neuromuscular transmission like aminoglycosides. Patients under serial casting for spasticity were also excluded from the study. Other exclusion criteria were pregnancy, neuromuscular disease like myasthenia gravis, and hypersensitivity to botulinum toxin. Generalized spasticity and profound cognitive impairment. Written, informed consent was obtained before participation. Each patient received 1 set of injections after baseline assessment and was reevaluated at 3, 12, and 24 weeks. Identification of the target muscle was made after a comprehensive assessment, including information from the patient, carer, and the treating therapist. Anatomical landmarks for motor point localization and injection were utilized according to standard electromyographic texts. Injections of botulinum toxin A (Botox, Allergen) were given via a 21–30-gauge needle. Vials of 100 U have diluted accordingly, e.g., for large muscle, we used greater dilution say 1:4 and for smaller muscles like intrinsic hand muscle, we used smaller dilution say 1:2. The doses and distribution of the injections were guided by the clinical and subjective rating of the problem. All patients had to participate in an active rehabilitation management program for at least 6 months. Five to 10 days before the clinic appointment, each patient was assessed with a combination of measurements. The primary outcome measure of impairment was the degree of resistance to passive movement of the target muscle group, which was assessed using the modified Ashworth scale of spasticity. The passive range of motion at the target joint was measured using a hand-held goniometer. To compare changes between patients treated for different joints (which have different degrees of movement), the change in the range was calculated by the percentage of normal passive range movement for each joint. For example, patients who were recorded as having 10° of wrist extension from the position of neutral and full flexion of (80°) would be said to have 60% range of movement at the joint (full range of flexion = 80°, full range of extension = 70; 90/150 = 60%). Assessment of dynamic length by modified Tardieu scale. This measures the point resistance of rapid velocity stretch R 1 value followed by a slow passive joint range of movement R^2 value. We had patients with clonus, which could be scaled on Modified Tardieu Scale. The primary disability measure was the subjective rating of problem severity. The patient and carer for its severity on the scale of one to seven, where one identified an extreme problem and seven identified no problem at all, rated this. To assess proximal and distal strength control and dexterity, we used the Motricity Index, which is primarily a measure of muscle strength in upper motor neuron lesions. This is a weighted score derived from the Medical Research Council grades. Six-limb movement was tested and scored for arm and leg. Six movements are pinch grip, elbow flexion, shoulder abduction, ankle dorsiflexion, knee extension, hip flexion. It is a well-validated measure of strength for upper motor neuron lesions specifically for stroke patients. We added two more movements to this index and used the same weighted scores as used for the respective opposite movement which is in the original Motricity Index. The additional movements are elbow extension and knee flexion. The patient is supine. Elbow extension is done with the shoulder at 90° adduction, neutral with regard to rotation arm is supported in a position perpendicular to the table the forearm is fully flexed. Now, the patient is asked to extend up to 90°. Patients with elbow pronated during the test were scored 14, i.e., the movement has seen but not full range. This was very useful to assess the gross motor function of the arm for those with spasticity of the elbow flexors and pronators. When these additional movements were used and scored their respective opposite movements were not scored. Though this measure is not validated for assessing gross motor, limb control, and dexterity in spasticity we found it very convenient and easy to administer in a busy outdoor setting.

A treatment goal was set at the time of injection by the treating team. As, e.g., an upper limb goal might be "able to grasp and

release an object". For the lower limb, a goal might be "to be keeping both feet on the floor while standing from sitting".

The intervention goal was evaluated on a simple 3-point scale (0 = not achieved; 1 = partially achieved; and 2 = achieved and maintained) at 12 weeks follow-up. All other measures were assessed at 3, 12, and 24 weeks. Data were analyzed only for those patients who completed the study follow-up period to avoid attrition bias. All the subjects were examined by two well-experienced observers. There could have been interobserver bias in the interpretation of spasticity grading, after calculating the kappa coefficient (*K*) and it was found agreement between the interpretation was more than 75% kappa coefficient (*K*) only included in the final interpretation.

Study Size

The primary aim was to determine the effect of botulinum toxin A on impairment (i.e., spasticity) and therefore sample was based on gross and fine motor changes detected on a specific scale The sample size was determined based on the Motricity Index as the primary outcome measures assuming that each patient would yield one set of upper limb group and one set of lower limb muscle group for comparison. On this basis, it was estimated that comparison would have to be between at least 29 upper limbs and lower limb muscle groups. [Therefore, at least 29 patients aiming to detect the difference of 6 in Motricity between muscle groups and with a standard deviation (S.D.) of, 5% probability of type I error ($\alpha - 0.05$) and 80% power ($1-\beta = 0.8$)].

Statistical Methods

To facilitate computation of data, categorical variables of the Modified Ashworth Scale were assigned numerical values, designated as "computed MAS score" in this study. (MAS value 0 = 1, MAS value 1 = 2, MAS value 1+ = 3, MAS value 2 = 4, MAS value 3 = 5, MAS value 4 = 6) similarly we had a "computed Modified Tardieu Scale"(cMT) here we took only the measure of quality of muscle reaction (X)[MT (X) value 0 = 1, MT (X) value 1 = 2, MT (X) value 2 = 3, MT (X) value 3 = 4, MT (X) value 4 = 5, MT (X) value 5 = 6.]

The treatment effect was determined by comparing the change score between week 0 and week 3, week 12, week 24. Week 3 was chosen as the primary endpoint as any antispastic effect of botulinum toxin A is well established by this time. Changes over time of clinical futures were analyzed by using the Friedman test for non-parametric variables (i.e., passive range of motion, modified Ashworth score, modified Tardieu scale, Motricity Index).

Analysis of variance for repeated measurements for the parametric ones (age, weight, duration of spasticity, units, number of sites).

Results

A total of 34 patients were enrolled in the study 25 were male and 9 patients were female. Eleven patients were ≤ 15 years of age, of them, 3 patients had 9 upper limb joint muscle group involvements. And 8 patients had 25 lower limb joint muscle group involvements. Twenty-three patients were >15 years of age, of them, 14 patients had 42 upper limb joint muscle group involvements. Ten patients had 24 lower limb joint muscle group involvements. Of the total number of patients enrolled 3 patients were lost after the 3 weeks post-baseline follow-up. All those lost at 3 weeks post-baseline follow-up belong to >15 year age-group, 2 of them had upper limb joint muscle group involvement and one had lower limb joint muscle group involvement. The mean age of the patients was 36.19 the mean duration of spasticity was 6.68 years, of them, 7 patients had a duration of spasticity for <1 year and 27 patients had spasticity for >1 year.

In the upper limb group, the mean size of the dose distributed into various muscles injected was the upper limb group the mean size of the dose distributed. Mean of the sites injected 2.85 (S.D. 1.27) units, quartile range of 2; mean dilution used was 3.08 with (S.D. 1.00) units, quartile range of 2.

In the lower limb group, the mean size of the dose was 40.41 (S.D. 12.49) units. Quartile range of 25.0. Mean duration of spasticity 3.64 (S.D. 3.01) units, quartile range of 5.84, and mean dilution used was 4.0 (S.D. 0.0) units, quartile range of 0.0.

Doses were guided by clinical experience. A useful clinical guide to doses can be found in Mitchell et al.[10]

Comparisons of significant change (either increase or decrease in numerical values) across the time period of the study were analyzed with Friedman's test for non-parametric variables. Yielded the following results.

Modified Ashworth Scale

For Modified Ashworth Scale, Mann–Whitney *U* test on the aggregate outcome scores compares groups post-baseline.

- The comparison of the effect of botulinum toxin A between lower and upper limb muscle groups at 3 weeks ($z = 0.21$, $p = 0.84$), at 12 weeks ($z = 0.21$, $p = 0.83$), and at 24 weeks ($z = 0.21$. $p = 0.83$). Comparison showed no significant better scores between the groups.

Modified Tardieu Scale

For the modified Tardieu scale, Mann–Whitney *U* test on the aggregate outcome scores compares groups post-baseline.

- Comparison between lower limb and upper limb muscle groups, post-baseline at 3 weeks ($z = 2.95$, $p = 0.003$), 12 weeks ($z = 2.34$, $p = 0.019$), and 24 weeks ($z = 2.21$, $p = 0.027$). The results showed significant improvement of scores of the spastic lower limb muscle group's dynamic length *X* at 3, 12, and 24 weeks in comparison to the upper limb muscle group.

Percentage Range of Motion

For the percentage range of motion, the Mann–Whitney *U* tests on the aggregate outcome score compare the group post-baseline.

- Comparison between lower limb and upper limb muscle groups, at 3 weeks ($z = -1.91$, $p = 0.06$), at 12 weeks ($z = -1.42$, $p = 0.16$), and at 24 weeks ($z = -1.43$, $p = 0.15$). No significant difference was noted between the groups.

Motricity Index

For Motricity Index, the Mann–Whitney *U* test on the aggregate outcome scores compares the groups' post-baseline.

- Comparison between lower limb and upper limb muscle, at 3 weeks ($z = 3.16$, $p = 0.002$), at 12 weeks ($z = 2.34$, $p = 0.02$), and at 24 weeks ($z = 2.22$, $p = 0.026577$), post-baseline showed significant difference of scores between the groups with a significant increase in motor ability in the lower limbs as detected by the Motricity Index at 3, 12, and 24 weeks.

Intervention Goal Attainment Scale

For the intervention goal attainment scale, the aggregate outcome scores compared the groups' post-baseline. A significant difference

of score was found when comparing scores between lower limb and upper limb muscle groups, which showed significant goal attainment by patients with lower limb muscle involvement, compared to upper limb post-BTX-injections.

- Comparison between lower limb and upper limb muscle groups ($z = 2.34$, $p = 0.0191$), post-baseline.

Discussion

The purpose of the study was to determine the clinical outcome in patients with spasticity after botulinum toxin A injections within a rehabilitation program (tailored according to patients). We intended to study the effect of the interventions across the time period of study post-baseline and to compare between patients with upper limb and lower limb muscle group involvement. To find out focal impairment we used Motricity Index.

Recruitment involved detailed analysis of specific problems with multidisciplinary assessment and careful follow-up. All patients received advice and guidance on targeting physical therapy to the problem and splinting advice was given where appropriate. Patients were put under intensive physical therapy for the ensuing 6 months post-BTX-A.

Primary Measure of Impairment

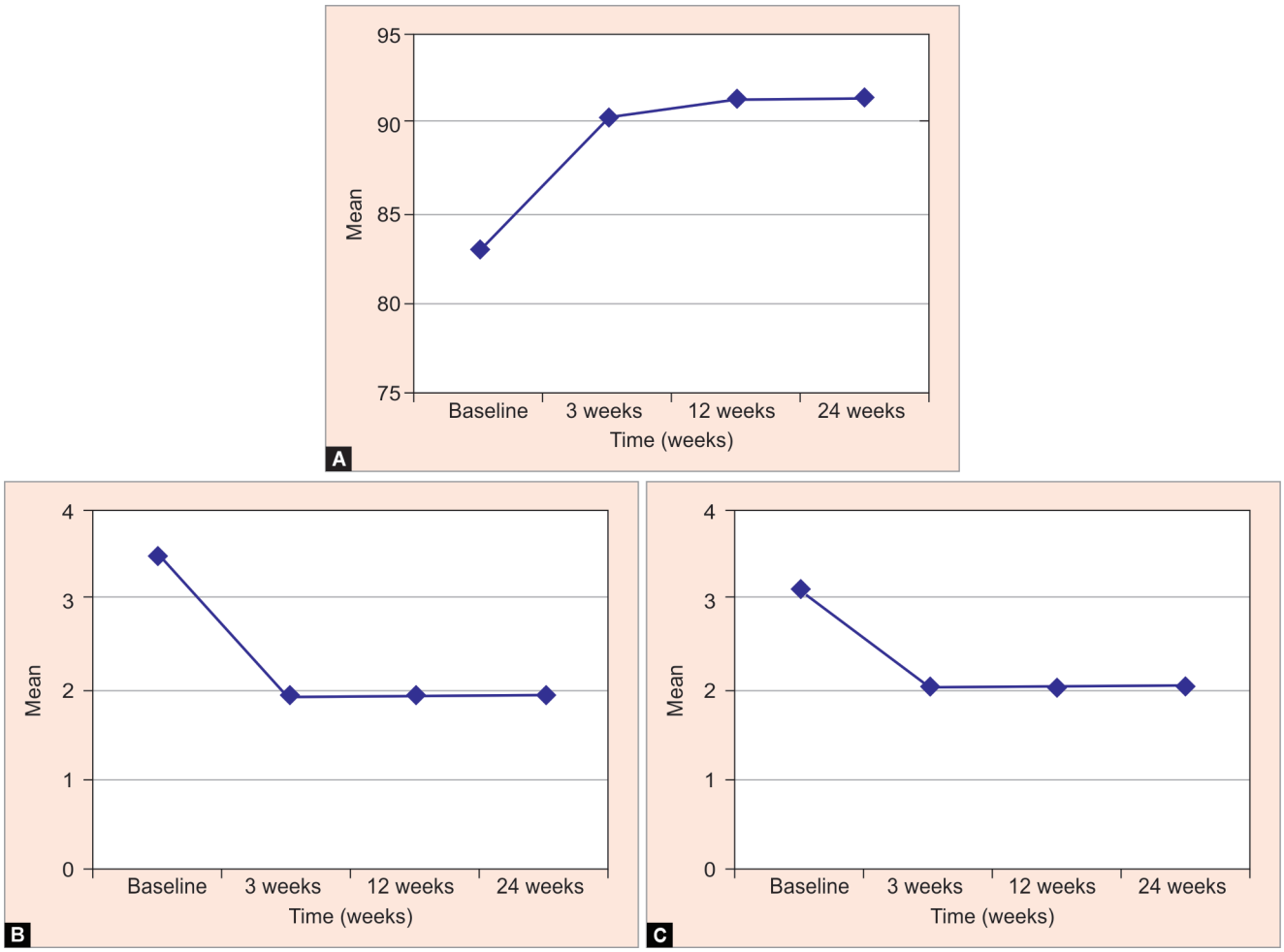
Benefits in impairment and focal disability were investigated. The primary measure of impairment was the measurement of muscle tone using the Modified Ashworth and Modified Tardieu Scale. The treated patients showed very significant improvement of score across the time period of the study post-baseline in all groups. Friedman's test was used for this. There was a significant improvement of Modified Tardieu scale scores for the lower limb as compared to the upper limb.

Secondary Measure of Impairment

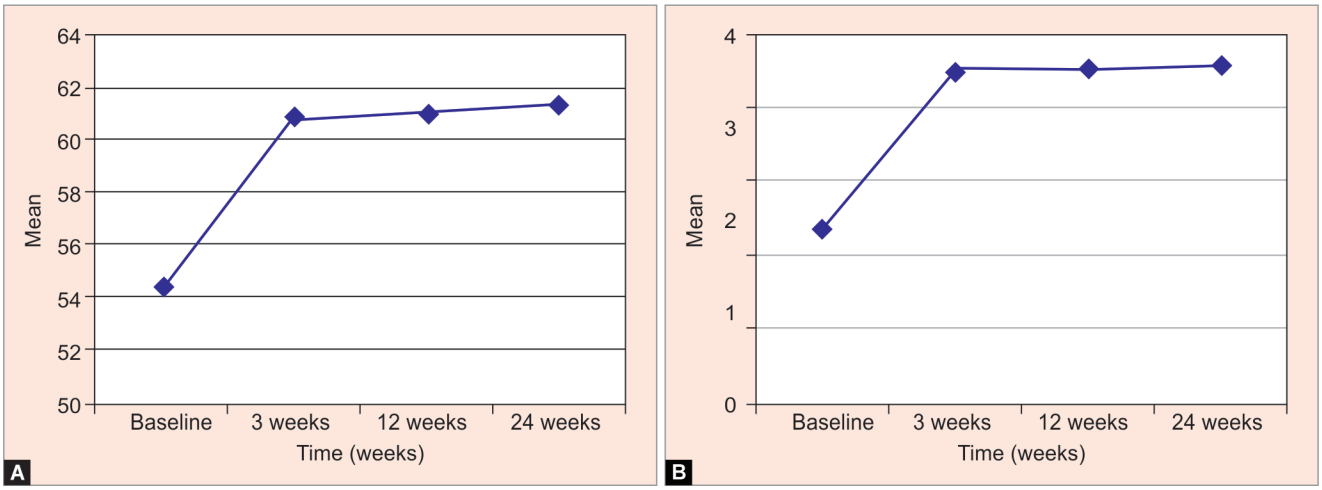
The passive range of motion was the secondary measure of impairment that is directly influenced by the degree of muscle tone. The results complement the Modified Ashworth and Modified Tardieu scores in that the greatest change in the passive movement occurred at the same time as the greatest change in the recorded Modified Ashworth and Modified Tardieu Scale over the 3 weeks as shown in Figure 1.

Primary Measure of Focal Disability

Patients or the carer's self-rating of problem severity measured the primary measure of focal disability. This showed a highly significant response to treatment across the time period of the study in all



Figs 1A to C: Secondary measure of impairment graphs depicting the decrease in modified Ashworth and Tardieu scores with a corresponding increase in percentage increase in range of motion at around 3 weeks time period



Figs 2A and B: Primary measure of focal disability graphs depicting an increase in Motricity Index with a corresponding increase in subjective ratings by a patient at around 3 weeks time period

the eight groups of patients studied. This is probably due to the specificity of the measure that evaluates the effect the toxin had on the presenting problem that the team identified as potentially amenable to treatment and therefore the most direct measure of the toxin on treatment. Furthermore, it does not rely on fixed endpoints and shows that the patient or the caregivers can detect the subtle improvements themselves.[11]

Of the standardized measures of focal disability, the Motricity Index showed a highly significant treatment effect across the time period post-baseline in all the eight groups studied. This is probably due to weighted scores being used in Motricity Index, which gives greater scores to movements that require dexterity and skill. Thereby increasing the specificity of the scale in detecting focal disabilities.[12]

The intervention goal attainment scale[13] used showed little difference between groups though there was very significant improvement across the time period of the study as shown in Figure 2.

Conclusion

It was concluded that botulinum toxin A has a definite effect on impairment and focal disability within the rehabilitation setup of selected patients with problems attributable to focal spasticity. Botulinum toxin A undoubtedly reduces the tone and increases the range of movement, which may lead to improvement in focal disability and subsequently create a favorable environment to initiate the patient into a rehabilitation program, for the overall functional benefit of the patient.

There was a significant improvement of all the non-parametric variables used in the study.

Comparison between upper and lower limb showed that there was significant improvement of lower limbs scores of the Modified Tardieu scale but the Modified Ashworth scale did not show a significant difference when compared between the groups. This indicates that for lower limb assessment of spasticity Modified Tardieu scale is more effective.

Comparison between lower and upper limb muscles showed a significant increase in motor ability for those with lower limb as determined by Motricity Index. So, Motricity Index may be a very useful tool in detecting changes in disability. This was also found useful to detect the secondary effect of reduction of hypertonia for which standardized and validated scales like FIM were not very sensitive according to most published reports.

Limitations

The heterogeneity of the group with recruitment with the inclusion of both adults and children and inclusion of different diseases under the umbrella symptom of spasticity and inclusion of upper and lower limb. Despite wide recruitment criteria, it was still difficult to achieve a large sample number. Perhaps the greatest limitation was that it was not possible to control the rehabilitation measures the patients were receiving before the inclusion into the trial.

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