A Randomized Control Trial of Botulinum Toxin A Administration under Ultrasound Guidance against Manual Palpation in Spastic Cerebral Palsy

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Background: Botulinum toxin A is established as an effective treatment to reduce spasticity in cerebral palsy (CP). But very little data are available regarding the techniques of administration. Hence, this study was conducted to compare administration of botulinum toxin with and without ultrasound.

Materials and Methods: This is a randomized trial conducted for 2 years at a tertiary care hospital in children aged up to 6 years with CP. Children were assessed with range of ankle dorsiflexion, Modified Ashworth Scale (MAS), and Gross Motor Function Measure 66 (GMFM 66) before and after administration. They were followed up for 6 months. Results: Of the 180 children screened, 30 who met the criteria were included. Those enrolled in the study were categorized into group I and group II, children who were given botulinum toxin with ultrasound (n = 14) and without ultrasound (n = 16), respectively. Results showed a significant increase in ankle dorsiflexion in both groups (P ≤ 0.005) but no significant difference was reported between the groups (P = 0.4). A statistically significant increase in GMFM scores (P ≤ 0.005) during sequential assessment was observed in both groups, but no significant difference was observed in the GMFM scores between the groups (P = 0.45). Majority of children improved by a scale of 2 (MAS) from baseline in groups after 12 weeks, 50% in group I and 57.9% in group II. Conclusion: No significant difference was observed in the outcome with regard to technique of administration of botulinum toxin with ultrasound and without ultrasound into gastrocnemius muscle.

Keywords: Botulinum toxin A, cerebral palsy, ultrasonography

INTRODUCTION

Cerebral palsy (CP) is described as a group of permanent disorders of movement and posture causing activity limitation, which are attributed to nonprogressive disturbances in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; by epilepsy; and by secondary musculoskeletal problems.[1] Population-based studies from around the world report prevalence estimates of CP ranging from 1.5 to more than 4 per 1000 live births or children of a defined age range.[2] Spasticity is a significant comorbidity in children with CP. Treatment of spasticity is essential to reduce pain, improve posture and movement, and decrease sequelae of contractures and deformity. Currently, various medications are available for the treatment of spasticity in children. These include oral muscle relaxants, intrathecal baclofen, and botulinum toxin.

Botulinum toxin is extracted from the bacteria Clostridium botulinum. Botulinum toxin A is an established and effective treatment to reduce spasticity in upper and lower extremities. Timely administration of botulinum toxin A in spastic CP will delay the...
development of contractures and alleviate the need for early surgical intervention. The American Academy of Neurology and the European Paediatric Neurology Society recommend botulinum toxin as the drug of choice for localized spasticity in CP.\textsuperscript{[3-6]} But very little data are available regarding techniques of administration. Though ultrasound-guided administration ensures accuracy, requirement of radiological setup and expertise is a disadvantage in this regard in our country. Our objective was to compare the efficacy of botulinum toxin when given with ultrasound guidance versus manual palpation in children with spastic CP.

**Materials and Methods**

This study is a prospective, single center, randomized interventional trial conducted for 2 years between May 2015 and May 2017 at a tertiary care hospital in Bengaluru, Karnataka, India. The study was approved by the institutional ethics committee. The study subjects were children, aged up to 6 years, with CP and spasticity as assessed by Modified Ashworth Scale (MAS) less than 4, attending the outpatient department. Children with fixed contractures and Gross Motor Function Measure (GMFM)\textsuperscript{[9]} 66 were excluded. An informed consent was obtained from the parents of study subjects. History and clinical examination using a systematically designed pro forma was noted. The tone was assessed by degree of ankle dorsiflexion, and extent of spasticity by MAS\textsuperscript{[8]} and Gross Motor Function Measure (GMFM)\textsuperscript{[9]} 66 was used to assess functional ability. Children were assigned to two groups by simple randomization technique.

Botulinum toxin A was administered into the gastrocnemius muscle under ultrasound guidance to one group and by manual palpation to the other group. It was administered to both limbs in double hemiplegics and diplegics and to single limb in hemiplegics. Adverse events were noted following administration and during follow-up visit. Physiotherapy was advised and reinforced at each visit at 4, 8, and 12 weeks. A feedback questionnaire with four-point ordinal scale was given to parents at 6-month follow-up for subjective assessment of effectiveness of botulinum toxin.

**Technique of injection:** The administration under ultrasound guidance was carried out in the ultrasound room. The marking for administration was assessed by a trained senior radiologist using MyLab 5 (Esaote, Maastricht, The Netherlands) with a frequency of 3–12 MHz. When the guidance was only clinical, the correct needle placement was verified by passively mobilizing the muscle. The product used was Botox produced by the Allergan Laboratory, in doses between 5 and 7 IU/kg. The dilution was carried out with 1 mL of 0.9% saline, and the reconstituted drug was injected at two sites into the belly of gastrocnemius muscle.

Clinical effectiveness was defined as a change of 5° in ankle dorsiflexion and a decrease of 1 in MAS, and functional improvement was defined by an increase in GMFM score by 6%. The results were analyzed using SPSS Inc. Release 2006. SPSS for Windows, Version 15.0, (Chicago, SPSS Inc.). The t-test was used to compare the two groups. We also used analysis of variance (ANOVA) for multifactor comparisons.

**Results**

A total of 180 children were screened and 30 children who met the inclusion criteria were included. The 30 children enrolled in the study were categorized into group I and group II, children who were given botulinum with ultrasound (n = 14) and without ultrasound (n = 16), respectively (Table 1 and Figure 1). Improvement in ankle dorsiflexion and MAS were assessed in each limb in both the groups, making n = 18 in group I and n = 19 in group II for ankle dorsiflexion and MAS. The two groups were matched with respect to age, sex, and topographical classification (Table 1). Children belonging to GMFCS II formed the majority in both groups, 78.6% in group I and 56.3% in group II. No change in the GMFCS level was observed after administration of botulinum in both groups. A statistically significant increase in GMFM scores (P ≤ 0.005) during sequential assessment was observed in both groups, but no significant difference was reported in the GMFM scores between the groups (P = 0.45) (Table 2).

The mean improvement in the angle of ankle dorsiflexion was found to be 11.7° and 15.7° in group I and II, respectively. RM ANOVA analysis showed a

### Table 1: Comparison of demographics

| Parameter                  | Group I | Group II | P value |
|----------------------------|---------|----------|---------|
| Age                        |         |          |         |
| 1–3 years                  | 7       | 7        | 1.0     |
| 3–6 years                  | 7       | 9        |         |
| Sex                        |         |          |         |
| Male                       | 9       | 10       | 1.0     |
| Female                     | 5       | 6        |         |
| Topographic classification  |         |          |         |
| Hemiplegia                 | 10      | 13       | 0.9     |
| Diplegia                   | 3       | 2        |         |
| Bilateral spastic CP       | 1       | 1        |         |
| GMFCS level                |         |          |         |
| I                          | 1       | 2        | 0.9     |
| II                         | 11      | 9        |         |
| III                        | 2       | 4        |         |
| IV                         | 0       | 1        |         |
A significant increase in both groups ($P \leq 0.005$) but no statistically significant difference was found between the groups ($P = 0.4$) [Table 3]. A decremental score of 1 to 3 was observed in MAS in this study. Majority of children improved by a scale of 2 from baseline in both groups after 12 weeks, 50% in group I and 57.9% in group II in this study. The mean feedback scores were similar in both the groups with a value of 17.4±1.7 and 17±1.5 in group I and II, respectively. Asthenia was reported by the physiotherapist in one child in group II, who eventually regained the tone. No other side effects such as pain, soreness at injection site, and anaphylactic reactions were noted in both the groups.

**DISCUSSION**

Botulinum toxin A has been proved to be an effective drug to relieve spasticity by multiple trials.[10,11] Various techniques of localization of muscle groups are available for administration of this drug. These include manual palpation, electrophysiological techniques, and
ultrasonography. In our study, we compared manual palpation with ultrasonographic guidance used to inject botulinum toxin into gastrocnemius muscle of children with spastic CP. The outcomes were measured in terms of change in ankle dorsiflexion, MAS, and functional improvement indicated by GMFM scores. Our study is the first Indian study regarding the technique of administration of botulinum toxin.

Py et al.\textsuperscript{[13]} conducted a similar study ($n = 54$) where they compared manual palpation with ultrasound-guided injection of botulinum toxin into multiple muscle groups. They found a functional improvement in 24% of children. The functional effectiveness was also improved by using ultrasound guidance ($P < 0.02$).\textsuperscript{[12]}

In our study, though all children showed significant improvement following administration of toxin, no significant difference was observed between the groups. This discordant outcome of our study was probably because gastrocnemius is a bulky muscle and does not need ultrasound guidance. Other muscle groups were also studied in the study conducted by Py et al.\textsuperscript{[12]}

Schroeder et al.\textsuperscript{[13]} summarized that manual needle placement could be inaccurate. Electrophysiological techniques are painful and time-consuming. They predicted that sonographic imaging has the potential to evolve into a procedure that may equal the electrophysiological techniques.\textsuperscript{[13]}

Berweck et al.\textsuperscript{[14,15]} performed more than 6000 sonography-guided injections of 70 different muscles in approximately 350 children. They recommended sonography for visually controlled, anatomically precise injection of botulinum toxin.\textsuperscript{[14]} Clear differentiation of structures adjoining the target muscle is possible using ultrasonography, and this prevents accidental injection into subcutaneous or intravascular sites.\textsuperscript{[14]}

A skilled personnel and equipment is required for the administration of botulinum toxin A under ultrasound guidance, but as ours is a tertiary care center, this was not a limitation in our study. The cost of ultrasound though adds to the expenses, it is an affordable intervention. No significant difference was observed in the outcome with regard to technique of administration of botulinum toxin with ultrasound and without ultrasound into gastrocnemius muscle. Limitations of our study were as follows: sample size was small and our conclusions were limited to gastrocnemius muscle and ultrasound guidance may be required for precise and accurate administration of botulinum to less bulky muscles.

**Conclusion**

No significant difference is observed in the outcome with regard to the technique of administration of botulinum toxin with ultrasound and without ultrasound into gastrocnemius muscle. Hence for the administration of botulinum toxin into gastrocnemius muscle, ultrasound guidance need not be mandatory. Botulinum toxin is a very effective method for the management of spasticity in CP.

**Acknowledgement**

We would like to thank Dr. Ramesh, professor at the Department of Radiology, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, for his guidance during the administration of botulinum toxin.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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