

# Comparison of Efficacy of Botulinum Toxin A and Intramuscular Ethyl Alcohol Injection on Gastrocnemius Muscle Spasticity and Functional Outcomes in Cerebral Palsy Patients - Double Blinded Randomized Clinical Study

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**Abstract:** *Study Design:* Double, blinded randomised clinical study. *Objective:* Most children affected with spastic diplegic cerebral palsy have motor disorder, spastics being the foremost common. Spastic CP is difficult to treat further more to rehabilitate. Among the varied modalities of treatment for spastic CP, ethyl alcohol and botulinum A has been gaining popularity because of their localised result, negligible general side effect, easy application and improved practical outcome of patient. Various studies are done over years on the advantages and practical outcome on use of ethyl alcohol and botulinum A in treating spasticity in CP patients, however there's lack of studies on the practical outcome on use of these agents. *Material and Method:* From 2016 to 2018, a total of seventeen sample legs were recruited with predominantly gastrocnemius spasticity in spastic CP patients and randomly divided into 2 groups of ethyl alcohol and botulinum A injections using computer generated random block organization. Group 1 was injected 50 % ethyl alcohol and group 2 got botulinum A - 4units/kg of bodyweight followed by five days of Above Knee cast in maximum dorsiflexion followed by physiotherapy and AFO splint. Pre and post intervention muscle spasticity and power, GMFM rating and active and passive Ankle Range of motion were recorded and follow up at 6 months. Statistical analysis was done by paired t test and continual multivariate analysis test (ANOVA). *Result:* There was no significant difference of improvement in spasticity among the each ethyl alcohol and botulinum toxin A group (37.5% vs 33.33% of patients) and significant improvement of gastrocnemius power in 75% of patients vs 11.11% of patients in ethyl alcohol group. There was no significant difference of improvement of GMFM score  $8.25 \pm 7.58$  in botulinum toxin A group vs  $7.85 \pm 4.63$  in ethyl alcohol group ( $p=0.916$ ). There was no significant difference of improvement of total passive Ankle ROM  $13.75 \pm 11.5$  in botulinum toxin A group vs  $16.59 \pm 15$  in ethyl alcohol group ( $p=0.663$ ) and improvement of total active Ankle ROM  $11.87 \pm 9.6$  in botulinum toxin A vs  $3.89 \pm 13.6$  in ethyl alcohol group ( $p=0.189$ ). *Conclusion:* There is comparable efficaciousness of 50% ethyl alcohol and botulinum toxin A in reducing gastrocnemius spasticity, GMFM scoring and total active and passive ROM in spastic CP patients.

## 1. Introduction

Cerebral palsy (CP) is a non-progressive neuro-muscular disorder of the developing immature brain which includes clinical syndrome of permanent motor abnormality of body posture or ambulation. The worldwide incidence of CP is approximately 2 to 2.5 cases per 1000 live births.<sup>1</sup> In India, it is estimated at around 3 cases per 1000 live births; however, being a developing country the actual figure may be much higher than probable figures. There are about 25 lakh CP children in India as per the last statistical information.<sup>2</sup>

Most children affected with CP have a motor disorder, spasticity being the most common. Spastic CP is challenging to treat as well as to rehabilitate. Spasticity hampers functionality of affected parts, also causing pain, disturbance in sleep-wake pattern, increased number of complications and morbidity, in turn causing increased dependence on family members and care givers, as well as burden to society.<sup>3</sup>

There is no defined and standardized approach for the management of spasticity in CP, but proper and adequate assessment of the presenting impairments causing disabilities should be done for appropriate treatment of the same. Generally the treatment protocol depends on the degree of functional limitations due to the underlying spasticity and its location.

Use of ethyl alcohol, phenol and Botulinum toxin A is gaining popularity in management of spasticity in CP due to their localized effect, minimal systemic side effects, ease of application and improved functional outcome of the patient when accompanied with splinting and regular physical and occupational therapy.

Various studies have been done over years on the benefits and functional outcome on use of ethyl alcohol and Botulinum toxin A in treating spasticity in CP, but there is lack of studies comparing the functional outcome on use of each of these agents.

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## 2. Methodology

Inclusion criteria were diagnosed cerebral palsy patients who were ambulatory of age more than 2 years. Spasticity in one or both gastrocnemius muscles of lower limb presenting with characteristic equinus position of foot and Observed spasticity score of 1 and above on the Modified Ashworth Scale.

The patients excluded from study were those having Evidence of fixed joint contracture, Previous surgery of lower limb or dorsal rhizotomy and current need for surgery, Presence of movement disorders other than spasticity, Previous injections of phenol or ethyl alcohol into the muscle to be injected and Current or previous therapeutic exposure to Botulinum Toxin A

Block randomization with varying block size generated by the computer was used to recruit the patients into the two study groups.

Both the groups received injections in Gastrocnemius muscle of the involved leg under full aseptic precautions in Minor OT.

Group 1 received 50% solution of Ethyl Alcohol, diluted with normal saline and 2% xylocaine in the ratio of 2:1:1(4ml+2ml+2ml=8ml). 2 ml of this solution was injected into each of four quadrants of gastrocnemius muscle with a 24G needle.

Group 2 received Botulinum Toxin A injection in 4 quadrants of gastrocnemius of the involved leg. Each injection was prepared by reconstituting one vial of Botulinum toxin A with 1 ml of sterile saline to achieve a concentration of 10 units/0.1 ml. A total dose of 4 units/kg body weight was injected to the gastrocnemius muscle of a participant with a 24G needle at 4 sites after reconstituting with desired volume of normal saline to make total volume of 8 ml of solution. 2 ml of solution was injected to each of the 4 quadrants of gastrocnemius muscle.

It was a double-blinded study, where both the participants and the observers were blinded.

Their Gross Motor Functional Classification System (GMFCS) grading was measured at baseline and 6 months follow-up. The functional outcomes were evaluated and recorded using:

### Primary Outcome Measure-

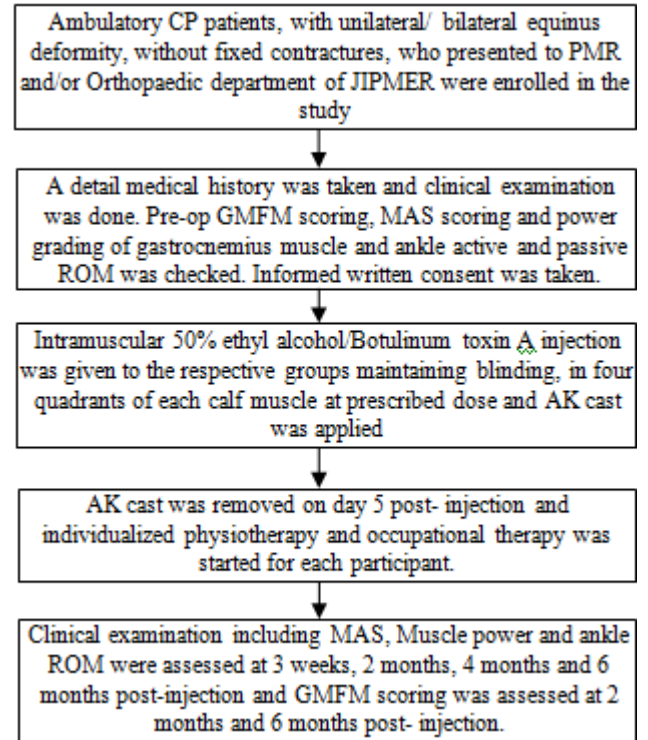
Gastrocnemius muscle spasticity [Modified Ashworth Scale (MAS)],

Gastrocnemius muscle power

### Secondary outcome Measure:

Ankle joint active and passive movement, and

Gross Motor Function Measure (GMFM-88 scoring)



**Figure 5:** The Procedure and Approach of Participants in the Study, Including Different Assessment Measures

## 3. Results

A total of 13 patients with 21 sample legs were recruited for the study but 2 patients with 4 sample legs were lost in follow up and hence excluded. Hence total of 11 patients with 17 sample legs were included in the study, randomized into two intervention groups, Botulinum Toxin A group and Ethyl Alcohol group, and followed up to a period of 6 months. Total of 4 patients with 8 sample legs were given Botulinum Toxin A injection and 7 patients with 9 sample legs were given 50% ethyl alcohol injection. 8 (73 %) among them were males and 3 (27%) females. Mean age of the patients was  $6.7 \pm 4$  years and mean weight of patients being  $17.4 \pm 6$  kg. 6 (54.54%) patients had bilateral involvement and 5 (45.46%) had unilateral involvement.

Along with Botulinum toxin A or Ethyl Alcohol injection to gastrocnemius muscle 3 patients underwent additional treatments which included injections in other muscle groups and surgical procedures. Out of 11 patients, 2 patients had history of seizure and were on anti-epileptic medication.

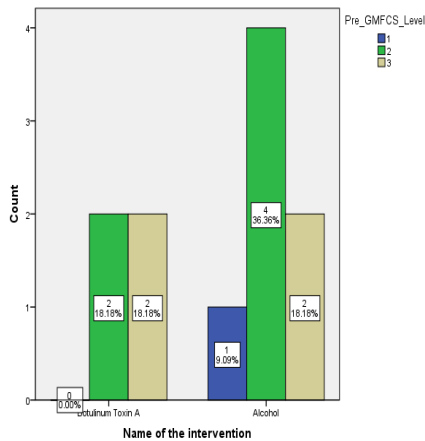


Figure 1: GMFCS\_Level at Baseline

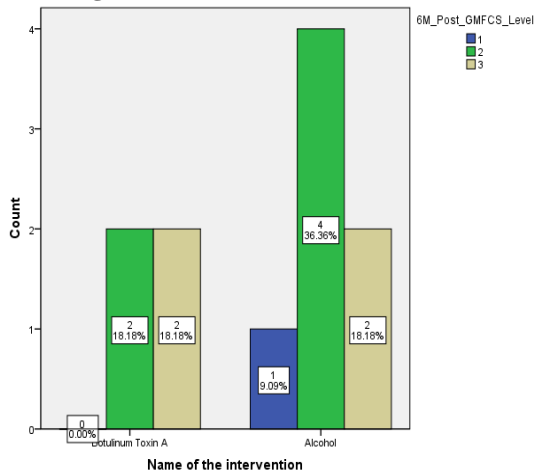


Figure 2: GMFCS\_Level at 6 Months Follow Up

Out of the total 11 patients recruited, 4 were in Botulinum Toxin A group in which 2 patients were in GMFCS level 2 and 2 patients were in GMFCS level 3, who continued to remain at same level at the end of the 6 month study period. 7 patients were allocated to ethyl alcohol group in which 1 patient was in GMFCS level 1, 4 patient were in GMFCS level 2 and 2 patients in GMFCS level 3, who continued to remain at same level at the end of the 6 month study period.

Spasticity by MAS: At the baseline, in the Botulinum toxin A group, 1 out of 8 (12.5%) patients were at level 1,2 and 3 and 7 out 8 (87.5%) patients belonged to level 4 and 5. Similarly in ethyl alcohol group, 6 out of 9 (66.67%) were at level 1,2 and 3; and remaining 3 out of 9 (33.33%) patients belonged to level 4 and 5.

After 6 months post-intervention, 1 out of 8(12.5%) patients in botulinum toxin group in levels 1-3 increased to 4 out of 8(50%) patients while, in ethyl alcohol group 6 out of 9(66.7%) patients in level 1-3 increased to 9 out of 9(100%) patients. Hence, there was improvement in 37.5% of patients in botulinum toxin and 33.3% of patients in ethyl alcohol groups, during the 6 month follow-up, in gastrocnemius spasticity.

Muscle power: At the baseline, in the Botulinum toxin A injection group, all 8 (100%) patients were at level MRC grading 1- 2. While in the ethyl alcohol group, 6 out of 9 (66.7%) were at level 1-2 and remaining 3 out of 9 (33.3%) patients belonged to level 3-5. After 6 months post-

intervention, in the Botulinum toxin A injection group; 6 out of 8(75%) patients improved in muscle power of MRC grading 3-5, whereas in the ethyl alcohol group; only one out of 6 patients improved in muscle power of MRC grading 3-5. Thus, there was improvement in 75% of patients in the Botulinum toxin A group whereas there was improvement in 11.1% of patients in the ethyl alcohol group, during the 6 months follow-up period, in gastrocnemius muscle power.

Table 1: GMFM Scores of Botulinum Toxin A and 50% Ethyl Alcohol Groups at Different Points of Time (Mean ± SD)

Group	Pre intervention (Mean ±SD)	2 Month Post intervention (Mean ±SD)	6 month post intervention (Mean ±SD)
Botulinum Toxin A	69.5±8.103	76±8.042	77.75±8.539
Alcohol	85.71±7.158	88.86±7.426	93.57±5.127

Variable	Botulinum Toxin (n=4)	Alcohol (n=7)	Statistical Significance (P value)
GMFM Score	8.25 ± 7.588	7.857 ± 4.67	p=0.916

There is a mean improvement of GMFM score by 8.25 in botulinum toxin A group versus 7.86 in ethyl alcohol group at 6 months follow-up as compared to baseline. This shows that the average improvement in GMFM scores was comparable (p=0.916) which was not statistically significant.

Table 2: Total Active Rom of Ankle of Patients in Botulinum Toxin A and 50% Ethyl Alcohol Groups at Different Points of Time (Mean ± SD)

Group	Pre-intervention	Post intervention			
		3 week	2 month	4 month	6 month
Botulinum Toxin A	27.5± 18.127	34.38± 14.745	36.88± 15.104	39.38± 11.783	41.25± 9.543
Alcohol	21.11± 12.444	30.00± 10.607	32.78± 12.276	35.36± 14.884	37.7± 11.211

Variable	Botulinum Toxin (n=4)	Alcohol (n=7)	Statistical Significance
Total Movement Active	13.75 ± 11.57	16.59±15	p=0.663

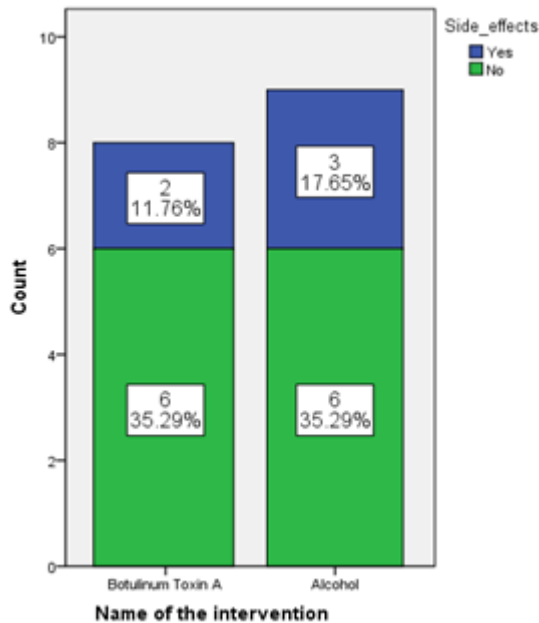
There is an average improvement of 13.75° in botulinum toxin A group versus 16.59° in ethyl alcohol group at 6 months of follow-up as compared to baseline. This shows that the average improvement in total active ROM was comparable (p=0.663), which was not statistically significant.

Table 3: Total Passive Rom of Ankle among Botulinum Toxin A and 50% Ethyl Alcohol Group at Different Time Points (Mean ± SD)

Group	Pre-intervention	Post intervention			
		3 week	2 month	4 month	6 month
Botulinum Toxin A	49.38 ± 12.082	54.38± 11.160	56.88± 13.346	61.25± 14.330	61.25± 14.330
Alcohol	43.89± 11.396	40.00 ±7.906	45.56± 9.825	48.89± 11.932	47.78± 9.052

Variable	Botulinum Toxin (n=4)	Alcohol (n=7)	Statistical Significance (P value)
Total Movement Passive	11.875± 9.613	3.8889± 13.6423	p =0.189

There is an average improvement of 11.87° in botulinum toxin A group versus 3.88° in ethyl alcohol group in 6 months follow-up, as compared to baseline. This shows that the average improvement in total passive ROM was comparable ( $p=0.189$ ) but not statistically significant.



**Figure 2:** Side effects among patients intervened with botulinum toxin a and ethyl alcohol injection

Out of 11 patients intervened, a total of 3 patients with 5 sample legs encountered certain side effects, in the post-intervention period. Out of these, 2 patients with 3 sample legs (17.65%) were given alcohol injection whereas 1 patient with 2 sample legs (11.76%) had received Botulinum Toxin A injection. The patients who received ethyl alcohol injection mainly suffered pain at the injection site, moderate grade intermittent fever, induration, and redness and swelling at injection site, whereas the patient who received Botulinum Toxin A had mild grade fever and pain at the injection site.

Further, on performing cost analysis, it was found that the average cost per sample site for treatment with Botulinum Toxin A was Rs 5250 whereas for treatment with alcohol, it was Rs 4 per sample site, suggesting that treatment with Alcohol is more cost-effective as compared to treatment with Botulinum Toxin A.

#### 4. Discussion

There was comparable beneficial improvement among the patient post Botulinum Toxin A and 50% Ethyl Alcohol injection with no significant superiority of one over another. But as ethyl alcohol was cheaper and easily available as compared to Botulinum Toxin A, ethyl alcohol was found to be cost effective than Botulinum Toxin A.

The goal of treatment of spastic equinus deformity of ankle, using 50% ethyl alcohol or Botulinum Toxin A, is to decrease the spasticity of gastrocnemius muscle with the improvement of its muscle power, thus increasing mobility of ankle in order to improve the functional daily activities of

the patients with an intention to help attain independent daily activities by the patients and postponing the requirement of surgery, bypassing the toxicity of other oral medications and inherent risks of surgeries.

There are various studies where Ethyl Alcohol and Botulinum Toxin A have been used as the primary treatment modality in the management of spastic equinus deformity of ankle in patients with cerebral palsy. Studies done by Tardieu et al<sup>4</sup> and Carpenter et al<sup>5</sup> showed reduction in gastrocnemius muscle spasticity after ethyl alcohol injection in spastic gastrocnemius muscle, which is consistent with the finding of improved gastrocnemius muscle spasticity after injection of 50% ethyl alcohol in this study. Individual studies using Botulinum Toxin A on spastic gastrocnemius muscle done by Colovic et al<sup>6</sup>, Barbaud et al<sup>7</sup>, Ackman et al<sup>8</sup> and Koog et al<sup>9</sup> showed significant improvement in gastrocnemius muscle spasticity, GMFM scoring and active and passive range of motion of ankle, as opposed to this study which showed no significant improvement in GMFM score but showed significant improvement in active and passive range of motion of ankle and reduction in gastrocnemius muscle spasticity after Botulinum toxin A injection.

The study done by Baghdadi et al<sup>10</sup> where they compared the efficacy of 45% ethyl alcohol with that of Botulinum toxin A injection on spastic calf muscles of cerebral palsy patients, found superiority of 45% ethyl alcohol over Botulinum toxin A in terms of improving range of motion of ankle, gait and daily activities of patients. This study, on the other hand, showed comparable efficacy of both 50% ethyl alcohol and Botulinum toxin A in terms of improvement in total active and passive range of motion of ankle and GMFM score.

The pre-injection state, functional ability of the patient, time devoted to physical therapy and occupational therapy, and the dedication of the parents or care givers towards the patient's care, have shown to be major factors in determining the outcome of patients. All the patients were kept under close observation and follow-up to assess the outcome variables and to observe how exercises are being carried out by them, and the care and dedication given by parents/care-givers.

The baseline GMFCS levels of the recruited patients and the GMFCS levels of the patient after 6 months were same for all patients regardless of the intervention. But some patients had fluctuation in GMFCS level during the follow-up period, mainly due to variability in care given by parents/care-givers, frequency of exercises during the day, compliance of patient in wearing AFO/KAFO during the study period, patient's mental status in understanding the importance of AFO/KAFO, exercises for functional improvement and prevention of involvement of other body parts. A study done by Yap et al<sup>11</sup> showed the importance of parent's care towards patients and the patient's willingness to have positive impact on improvement in performing daily activities and overall development of patients.

The conventionally used drug Absolute Ethyl Alcohol and more recently introduced Botulinum Toxin A have been the frontier modality of treatment for patients with gastrocnemius muscle spasticity causing dynamic equinus

deformity. The ease of application with minimal side effects, maximum output and higher compliance has made both drugs preferable and of choice in management of spasticity in patients with cerebral palsy. The low cost of alcohol, easy availability and low antigenicity property of alcohol has made it more used mode of treatment especially in India, as compared to Botulinum Toxin A which is expensive, not easily available and has chance of antibody formation on repeated use.

## 5. Conclusion

There is comparable efficacy of 50% ethyl alcohol and Botulinum toxin A in reducing gastrocnemius muscle spasticity, GMFM score and total active and passive ROM of ankle of patients. Side effects were found in both groups with them being slightly higher with 50% ethyl alcohol group. 50% ethyl alcohol is found to be more cost effective as compared to Botulinum toxin A.

We recommend the use of either 50% ethyl alcohol or Botulinum toxin A for treatment of gastrocnemius muscle spasticity while 50% ethyl alcohol being more favourable in a low resource setting like India due to its cost effectiveness and easy availability. As our study size was relatively small, further study on a larger population needs to be carried out to have a better analysis of the intervention.

## 6. Limitations of the Study

The limitation of this study is that Small study sample size due to short study period and limited patient pool at the hospital during the study period, short follow up period due to limited study period, thus making it inconvenient to assess long term outcomes and also, dynamic gait analysis could not be done during the follow-up period due to limitation of resources and technical issues.

## Data Archiving

There was no data to deposit.

## 7. Conflict of Interest

The authors declare no conflict of interest.

## 8. Acknowledgements

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