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Glycopyrronium Bromide is superior to Trihexyphenidyl for Reducing Drooling in Children with Cerebral Palsy—An Unregistered Randomized Controlled Trial

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Abstract

Background: Cerebral palsy is frequently associated with drooling or anterior sialorrhoea. This study was aimed to compare the efficacy of Glycopyrronium bromide and Trihexyphenidyl to reduce drooling in children with cerebral palsy (CP).

Materials and Methods: A single-centered, unregistered, randomized controlled trial was conducted from January to December 2022 on 100 children (aged 3–14 years) diagnosed with CP. The patients receiving conservative therapy without any medical or surgical intervention were included in the study. The study subjects were divided into two groups: 50 received oral glycopyrronium bromide, and 50 received oral trihexyphenidyl. Glycopyrronium bromide was administered starting at 0.02 mg/kg three times daily, titrated up to 0.1 mg/kg. Trihexyphenidyl was administered starting at 1 mg daily, increasing to a maximum of 2 mg three times a day. Follow-ups were conducted at 1, 3, and 6 months to assess drooling severity and frequency using the Thomas Stonell and Greenberg drooling rating scale.

Results: Glycopyrronium bromide was found to be more effective at 3 months in terms of only frequency (p= 0.02) but in terms of severity, which was statistically not significant. And at 6 months in terms of both frequency (p=0.00.9) and severity (p=0.001) of drooling was significantly improved with glycopyrronium bromide in comparison to trihexyphenidyl.

Conclusion: Oral glycopyrronium bromide was found to be significantly more effective than trihexyphenidyl at 3 months and 6 months to reduce drooling in children with cerebral palsy and side effects of both drugs are almost similar.

Keywords: Cerebral Palsy, Drooling, Glycopyrronium bromide, Trihexyphenidyl, Children , Thomas Stonell and Greenberg drooling rating scale

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Introduction:

Cerebral palsy (CP) is the most common cause of motor impairment in children[1] results from a nonprogressive brain injury that occurs during brain development. A frequent issue in CP patients is drooling, or anterior sialorrhea, the involuntary release of saliva from the mouth. [1] Children with CP often continue to drool up to the age of 18-24 months when it is expected to stop. Drooling in CP patients may lead to physical and psychological challenges. Treatment for drooling in CP is often multidisciplinary, with the aim of reducing excessive salivation while maintaining the oral cavity

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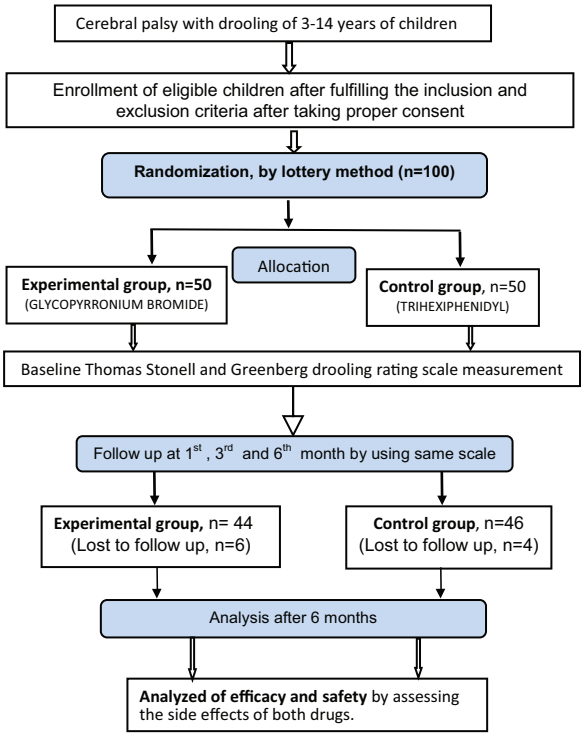
healthy. Positioning, oral-motor therapy, speech therapy, oral prosthetic devices, and pharmacological therapy are examples of noninvasive techniques.[2] Less invasive treatments include salivary gland duct photocoagulation, injection of botulinum toxin[3] and invasive techniques are radiotherapy and surgery.[2] The glycopyrronium bromide is an oral anticholinergic medication to treat drooling in children between the ages of 3 and 16,[4,5] and trihexyphenidyl, another anticholinergic drug often prescribed for dystonic movement disorders as well as reduction of drooling. Trihexyphenidyl works by reducing acetylcholine release from the basal ganglia, thereby improving motor-controlled fluidity. The objectives of this study were to compare the efficacy and side effects of glycopyrronium bromide and trihexyphenidyl in reducing drooling in children with cerebral palsy.

Materials and Methods:

This was an unregistered randomized controlled trial, conducted among the children aged 3–14 years with cerebral palsy-associated drooling at the Pediatric Neurology outpatient department, National Institute of Neurosciences and Hospital (NINS), Dhaka, from January to December 2022. The sample size was calculated via the following formula: n. A total of 100 cases, 50 in each group, were enrolled based on inclusion and exclusion criteria. Children aged 3–14 years with a primary diagnosis of cerebral palsy associated with drooling and patient previously received conservative and oral-motor therapy but did not receive any medical/surgical treatment for drooling and had not received any investigational drugs within 30 days of study entry were included in the study. Children with medical conditions contraindicated for anticholinergic therapy, known hypersensitivity to both medicines, poorly controlled seizures (defined as daily seizures), and a history of intestinal obstruction were excluded from the study. Randomization of study subjects of both the control and experimental group were ensured by using a numbered card. The control group received trihexyphenidyl, and the experimental group received glycopyrronium bromide. Data were collected via a structured questionnaire and analyzed using SPSS (version 25), with $p<0.05$ considered statistically significant. Ethical approval was obtained, and informed consent was secured from parents/caregivers. The study group received oral glycopyrronium bromide solution (syp.supotaria 1mg/5 ml) 0.02 mg/kg three times daily after a meal, followed by titration in increments of 0.02 mg/kg every 7 days for 4 weeks to an optimal maintenance dose of 0.1 mg/kg, but not exceeding 3 mg three times daily. The control group received oral trihexyphenidyl (syp.Hexinor 2mg/5ml), 1 mg once daily for 1 week, which was increased every week to an initial maximum of 2 mg of TDS. Follow-up was done through patients visit. Patients who were unable to attend were followed up by phone calls. Drooling severity and frequency were assessed by using the Thomas Stonell and Greenberg Drooling Rating Scale at baseline and at 1, 3, and 6 months. Drug compliance, effectiveness, and side effects were monitored. During titration, dose adjustments or pauses were made if tolerability issues arose.

Consort diagram:



Results:

Of the 100 enrolled children, 10 were lost to follow-up within one month, leaving 44 in the experimental group and 46 in the control group. The mean age was comparable between groups (6.33 ± 2.98 vs 5.98 ± 3.30 years; $p = 0.57$), with an overall mean age of 6.15 ± 3.13 years. Spastic quadriplegic cerebral palsy was the most common type in both groups, followed by spastic hemiplegia in the experimental group and spastic diplegia in the control group.

Most children in both groups had birth weights e"2.5 kg. Baseline characteristics, including feeding difficulty, speech delay, and cognitive delay, were comparable between groups, with significant differences only in weight and height/length. Multiple comorbidities were common.

Constant and frequent drooling was significantly greater in the spastic quadriplegic CP (p= 0.007). Occasional drooling was similar in spastic diplegic and hemiplegic CP (Table II). Severe drooling was more common in spastic quadriplegic CPs (51.1%), moderate drooling was more common in diplegic CPs (78.9%) and hemiplegic CPs (50.0%), and mild and profuse drooling was more common in dyskinetic CPs (Table III).

At baseline, moderate drooling was more common in the trihexyphenidyl group (60%) than in the glycopyrronium group (42%), with equal rates of profuse drooling (16%). After six months, drooling severity decreased in both groups but was significantly lower with glycopyrronium, with 61.4% versus 21.7% drooling-free ($p < 0.001$) (Table IV).

Drooling decreased more with glycopyrronium than trihexyphenidyl. Although not significant at one month ($p = 0.096$), significantly more children were drooling-free at three months (40.9% vs 21.7%, $p = 0.02$) and six months (68.2% vs 32.6%, $p = 0.009$) (Table V).

Among the 90 children enrolled (44 in the glycopyrronium group and 46 in the trihexyphenidyl

Table-I

Demographic characteristics of the study groups at the beginning (N=100)

	Group		p-value
	Experimental (Glycopyrronium) n=50(%)	Control (Trihexyphenidyl) n=50(%)	
Birth weight			
<1500g	4 (8.0)	8 (16.0)	0.284
1500-2499g	16 (32.0)	19 (38.0)	
>2500	30 (60.0)	23 (46.0)	
NVD	42 (84.0)	42 (84.0)	1.000
LUCS	8 (16.0)	8 (16.0)	
Perinatal asphyxia	47 (94.0)	47 (94.0)	1.000
Feeding difficulty	41(82.0)	44(88.0)	
Chewing difficulty	36 (72.0)	37 (74.0)	0.636
Swallowing difficulty	5 (10.0)	6 (12.0)	
Epilepsy	27(54)	30(60)	0.545
Weight	18.40 ± 8.24 (7.50 - 42.00)	14.21 ± 6.16 (7.00 - 35.00)	0.005
Height/Length	111.31 ± 21.38 (80.00 - 200.00)	103.26 ± 17.88 (78.00 - 150.00)	0.047
Spastic hemiplegia (30)	20 (40.0)	10 (20.0)	
Spastic diplegia (19)	6 (12.0)	13 (26.0)	0.298
Spastic quadriplegia (45)	21 (42.0)	24 (48.0)	
Dyskinetic, (6)	3 (6.0)	3 (6.0)	

Table-II

Drooling frequency in study subjects at the beginning among different types of CP (N=100)

	Spastic hemiplegia	Spastic diplegia	Spastic quadriplegia	Dyskinetic	p-value
Occasionally drools	17 (56.7)	11 (57.9)	9 (20.0)	3 (50.0)	0.007
Frequently drools	8 (26.7)	7 (36.8)	17 (37.8)	2 (33.3)	
Constantly drools	5 (16.7)	1 (5.3)	19 (42.2)	1 (16.7)	

Chi-Square test was done

Table-III

	Mild(%)	Moderate(%)	Severe(%)	Profuse(%)	p-value
Spastic hemiplegia	6(20.0)	15(50.0)	7 (23.3)	2(6.7)	0.001*
Spastic diplegia	3(15.8)	15(78.9)	1(5.26)	0(0.0)	
Spastic quadriplegia	2(4.4)	17(37.7)	23(51.1)	3(6.7)	
Dyskinesia	3(50.0)	2(33.3)	0(0.0)	1(16.7)	

Chi-Square test was done

* p-value was calculated by Chi-Square test ($p<0.05$ was considered significant)

Table-IV

Drooling severity at baseline, after one month, three months, and six months based on Thomas Stonell& Greenberg drooling rating scale between groups (N=90)

		Experimental (Glycopyrronium) n=44(%)	Control (Trihexyphenidyl) n=46(%)	
Baseline(E:C=50:50)	Dry	0(0.0)	0(0.0)	0.235
	Mild	5(10)	2(4)	
	Moderate	21(42)	30(60)	
	Severe	16(32)	10(20)	
	Profuse	8(16)	8(16)	
One month(E:C=44:46)	Dry	5(11.4)	0(0.0)	0.092
	Mil	11(25)	14(30.4)	
	Moderate	19(43.2)	18(39.1)	
	Severe	8(18.2)	14(30.4)	
	Profuse	1(2.3)	0(0.0)	
Three month(E:C=44:46)	Dry	18 (40.9)	10 (21.7)	0.074
	Mild	15 (34.1)	15 (32.6)	
	Moderate	8 (18.2)	19 (41.3)	
	Severe	3 (6.8)	2 (4.3)	
	Profuse	0(0.0)	0(0.0)	
Six month(E:C=44:46)	Dry	27 (61.4)	10 (21.7)	0.001
	Mild	9 (20.5)	17 (37.0)	
	Moderate	6 (13.6)	18 (39.1)	
	Severe	2 (4.5)	1 (2.2)	
	Profuse	0	0	

Table-V

Drooling frequency before and after treatment based on Thomas Stonell& Greenberg drooling rating scale between groups (N=90)

		Experimental (Glycopyrronium) n=44(%)	Control (Trihexyphenidyl) n=46(%)	p-value
Baseline(E:C=50:50)	Never: No drools	0(0.0)	0(0.0)	0.334
	Frequently drools	21(42)	28(56)	
	Constantly drools	24(48)	17(34)	
	Occasionally drools	5(10)	5(10)	
One month(E:C=44:46)	Never: No drools	5(11.4)	0(0.0)	0.096
	Occasionally drools	11(25.0)	16(34.8)	
	Frequently drools	19(43.2)	18(39.1)	
	Constantly drools	9(20.5)	12(26.1)	
Three month(E:C=44:46)	Never: No drools	18(40.9)	10(21.7)	0.02
	Occasionally drools	15(34.1)	17(37.0)	
	Frequently drools	8(18.2)	19(41.3)	
	Constantly drools	3(6.8)	0 (0.0)	
Six month(E:C=44:46)	Never: No drools	30 (68.2)	15 (32.6)	
	Occasionally drools	8 (18.2)	16 (34.8)	
	Frequently drools	5 (11.4)	13 (28.3)	0.009
	Constantly drools	1 (2.3)	2 (4.3)	

Chi-Square test was done; E=experimental, C=control

Table-VI

Comparison of adverse effects encountered by children in two groups (N = 90)

Adverse effects	Experimental group (Glycopyrronium) n = 44, n (%)	Control group (Trihexyphenidyl) n = 46, n (%)	p-value
Irritability, hyperactivity, restlessness	19 (43.2)	12 (26.1)	0.130[a]
Constipation	8 (18.2)	10 (21.7)	0.603[a]
Diarrhoea	5 (11.4)	4 (8.7)	0.727[b]
Dry mouth	5 (11.4)	3 (6.5)	0.712[b]
Vomiting	4 (9.1)	1 (2.2)	0.169[b]
Urinary retention	3 (6.8)	3 (6.5)	1.000[b]
Fever	2 (4.5)	3 (6.5)	0.646[b]
Other	1 (2.3)	2 (4.3)	1.000[b]

[a]Chi-square test was used, [b]Fisher's exact test was used

group), no statistically significant difference was observed in the frequency of adverse effects between the two groups ($p > 0.05$).

Discussion:

The aim of this study was to evaluate the efficacy of glycopyrronium bromide versus trihexyphenidyl to reduce drooling in children with cerebral palsy aged 3–14 years (mean 6.15 ± 3.13 years). Similar studies, including those by Zeller et al., Parr et al., Chavez et al., and Hedge et al., reported a predominance of male patients. [5-8] In our study, males predominated in the experimental group (68%), while females predominated in the control group (56%). All patients were developmentally delayed, unlike

the 31.6% reported by Rio et al.[9], likely reflecting differences in early intervention programs. Spastic quadriplegic CP was the most common type in our study (45%), followed by hemiplegic (30%), diplegic (19%), and dyskinetic CP (6%), consistent with previous reports. Hedge et al.[6] also found quadriplegia most prevalent, while hemiplegia was least common; in our study, hemiplegia was the second most frequent type. Drooling severity showed no significant improvement at one and three months in either group, but by six months, there was a significant reduction. The proportion of children who never drooled was higher with glycopyrronium than trihexyphenidyl (61.4% vs 21.7%, $p = 0.001$). These results align with previous studies: Bachrach et al.[10] reported 95% improvement with glycopyrronium, Reid et al.[11] observed 85% improvement with glycopyrronium versus 75% with trihexyphenidyl, Mier et al.[12] reported 87% improvement with glycopyrronium, and Zeller et al. found 73.7% efficacy.[13] In contrast, Rio et al.[9] reported only 60.4% improvement with trihexyphenidyl, lower than observed in our study.

Regarding safety, glycopyrronium had more adverse effects than trihexyphenidyl, including irritability/ restlessness (38% vs 24%), diarrhea (10% vs 8%), and dry mouth (10% vs 6%), while constipation was more common with trihexyphenidyl (20% vs 16%). These findings are consistent with Mier et al.[12], who reported irritability as the main side effect of glycopyrronium, but differ from Reid et al.[11], who found fewer adverse effects with glycopyrronium. Rio et al. also reported constipation as the major side effect of trihexyphenidyl (42.6%).[9] Overall, this study demonstrates that glycopyrronium is more effective than trihexyphenidyl in reducing drooling in children with cerebral palsy, with an acceptable safety profile, though mild adverse effects are more frequent.

Limitations of the study: Small sample size, Lack of placebo-control , Single center study, Non-blinded design.

Conclusion

Glycopyrronium bromide was found more efficacious than Trihexyphenidyl for reducing drooling in children with cerebral palsy. Almost equal and minor adverse effects were found while using glycopyrronium bromide & trihexyphenidyl to reduce drooling.

Further recommendation

Multi-center, large-scale, placebo-controlled, double-blinded studies are recommended for further information.

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