frontiers | Frontiers in Neurology

TYPE Brief Research Report
PUBLISHED 25 July 2022
DOI 10.3389/fneur.2022.922333

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

RECEIVED 17 April 2022
ACCEPTED 05 July 2022
PUBLISHED 25 July 2022

CITATION
Matsumoto S, Koizumi H, Shimazu H, Kaji R and Goto S (2022) A dual dopaminergic therapy with L-3,4-dihydroxyphenylalanine and chlorpromazine for the treatment of blepharospasm, a focal dystonia: Possible implications for striosomal D1 signaling. *Front. Neurol.* 13:922333. doi: 10.3389/fneur.2022.922333

A dual dopaminergic therapy with L-3,4-dihydroxyphenylalanine and chlorpromazine for the treatment of blepharospasm, a focal dystonia: Possible implications for striosomal D1 signaling

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Impairment of balanced activity between dopamine D1 and D2 receptor functions in the striatum, particularly in striatal functional subdivisions (i.e., striosome and matrix compartments), has been proposed to underlie dystonia genesis. This study was undertaken to examine the therapeutic effect of dual dopaminergic modulation with L-3,4-dihydroxyphenylalanine (L-DOPA) and chlorpromazine (CPZ) in patients with blepharospasm, a focal dystonia. For this purpose, Dopacol tablets^{TM} (L-DOPA 50 mg plus carbidopa 5 mg) and Wintermin^{TM} (CPZ phenolphthalinate 180 mg/g) were used. Clinical evaluations were performed before and after an 8-week drug treatment interval using the Visual Analog Scale (VAS), Blepharospasm Disability Index (BSDI), modified VAS (mVAS), and Jankovic Rating Scale (JRS). The data were analyzed using non-parametric statistics. Results showed that in patients ($n = 7$) with blepharospasm, dystonia symptoms were significantly alleviated by the administration of both Dopacol tablets^{TM} (one tablet × 3/day) and CPZ (5 mg × 3/day), as determined using the VAS, BSDI, mVAS, and JRS. In contrast, there was no improvement of dystonia symptoms in patients ($n = 7$) who ingested Dopacol tablets^{TM} (one tablet × 3/day) alone, nor in those ($n = 7$) who ingested CPZ (5 mg × 3/day) alone. Thus, dual pharmacotherapy with L-DOPA and CPZ can exert a therapeutic effect on blepharospasm, suggesting

that dystonia symptoms can be attenuated through dopaminergic modulation with inducing an increase in striatal D1-signals. Since dopamine D1 receptors are heavily enriched in the striosome compartment in the "human" striatum, our results also suggest that striosomal loss of D1-signaling may be important in the pathogenesis of dystonia.

KEYWORDS

blepharospasm, dystonia, L-DOPA, chlorpromazine, dopamine D1 receptor, striatum, striosome compartment, patients

Introduction

Blepharospasm is the most frequent phenotype of focal dystonia in adults and manifests as excessive blinking and spasms of the eyes (1–3). The reported prevalence of blepharospasm ranges from 20 to 133 cases per million individuals (4).

The symptoms of blepharospasm are often severe enough to result in functional blindness (5–7). Botulinum toxin (BTX) injection into the orbicularis oculi muscles is now considered as the first-line treatment for blepharospasm (8); however, it often produces unsatisfactory results (9, 10). Administration of anticholinergics, benzodiazepines, baclofen, or tetrabenazine can also be therapeutic options (11), but these frequently cause serious side effects as well as failure of therapy (12, 13). The currently available oral pharmacotherapy can be limited by the common occurrence of adverse effects, which contribute to a decrease in compliance or discontinuation even before benefits are evident (11). Therefore, the development of alternative or adjunct pharmacotherapy for the treatment of blepharospasm is required (3, 11).

Impairment of balanced activity between dopamine D1- and D2-like receptor (D1R and D2R) functions in the striatum, which consists of two functional subdivisions called the striosome (patch) and matrix compartments (14), has been proposed to underlie dystonia genesis (15–18). The striosome and matrix dopamine systems play central roles in cortico-thalamo-basal ganglia circuits and are thought to underlie the genesis of multiple movement and behavioral disorders (18–20). A recent modular computational model of the basal ganglia network suggested that striosomal dysfunction may induce inappropriate "motor action selection" and promote specific repetitive, stereotyped behaviors, including dystonia symptoms (21). This hypothesis is supported by the functional anatomy observed in several human disease models. For instance, mutations in the *GNAL* gene, which encodes the stimulatory α subunit of the G-protein (Gαolf), cause primary torsion dystonia (22), known as DYT25 dystonia (Figure 1, DYT25). Gαolf is highly expressed in the striatum (23, 24), where it couples D1Rs in direct pathway medium spiny neurons (MSNs) and adenosine A2A receptors in indirect pathway MSNs to increase 3′,5′-cyclic AMP (cAMP) through activation of adenylyl cyclase type 5 (23, 24). This indicates that in DYT25, loss of Gαolf function induces a decrease in the cAMP level in both the D1-direct and D2-indirect pathway MSNs, leading to the reduced activity of D1Rs in direct pathway MSNs and enhanced activity of D2Rs in indirect pathway MSNs. Given that both D1Rs and Gαolf are highly concentrated in striosomes (18, 25), DYT25 dystonia also represents a loss of striosomal D1-signal activity. Furthermore, in patients with X-linked dystonia-parkinsonism, also known as DYT3 (Figure 1, DYT3), postmortem analyses revealed a predominant loss of D1R-expressing MSNs in the striosomes relative to the matrix compartment in the early disease phase when dystonia symptoms occur (15, 17). Thus, loss of D1-signaling in the striosome compartment may cause dystonia symptoms, at least in part, in dystonia syndrome.

This study was undertaken to examine whether dystonia symptoms can be attenuated through dopaminergic modulation, which induces an increase in striosomal D1-signaling. In line with our immunohistochemical studies on human autopsied brains, we have shown that in the neostriatum, D1R proteins are heavily enriched in striosomes, while these are modestly distributed in the matrix compartment (26). This indicates that when D1 agonists are administered orally, they preferentially act on the striosome compartment in the "human" striatum. Here, we sought to determine whether dual dopaminergic therapy with L-3,4-dihydroxyphenylalanine (L-DOPA) and chlorpromazine (CPZ) exerts a therapeutic effect on blepharospasm. L-DOPA is the direct precursor of dopamine (27), the full agonist of both D1Rs and D2Rs, whereas CPZ is an effective antagonist of D2Rs (28).

Abbreviations: L-DOPA, L-3,4-dihydroxyphenylalanine; CPZ, Chlorpromazine; VAS, Visual Analog Scale; BSDI, Blepharospasm Disability Index; mVAS, Modified Visual Analog Scale; JRS, Jankovic Rating Scale; BTX, Botulinum Toxin; D1R, dopamine D1 like receptor; Gαolf, olfactory type G-protein α subunit; MSNs, Medium Spiny Neurons; cAMP, 3′,5′-cyclic AMP; D1Rs and D2Rs, dopamine D1- and D2-like receptors; DOPACOL, Dopacol tablets L50 TM (50 mg of L-DOPA plus 5 mg of carbidopa; Nichi-Iko Pharmaceutical Co., Ltd. Toyama, Japan); D2R, dopamine D2 like receptor.

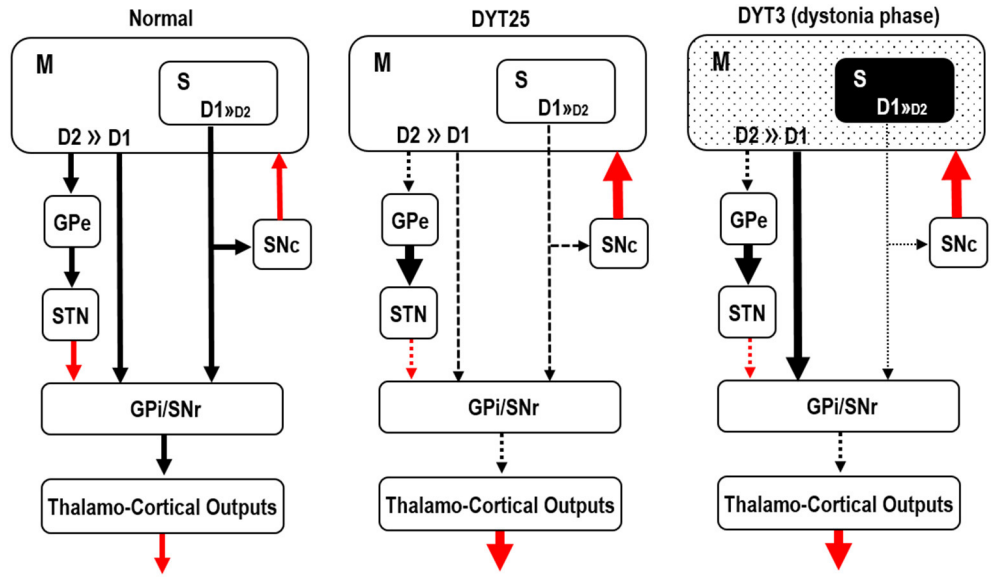

FIGURE 1
Hypothetical functional anatomy of the basal ganglia in DYT25 and DYT3. A schematic representation of the basal ganglia circuit is presented. Black and red arrows indicate inhibitory and excitatory striatal output projections, respectively. The striatum consists of two functional subdivisions: striosome (S) and matrix (M) compartments. Three major pathways are emphasized: the direct pathway originating from medium spiny striatal projection neurons (MSNs) possessing D1-receptors (D1), the indirect pathway from MSNs possessing D2-receptors (D2), and the striosomal pathway from the striosome (S) compartment, which is heavily enriched in D1-receptors. In DYT 25, mutations in the *GNAL* gene cause a loss of function of Gαolf, leading to reduced activity of D1-receptors in striosomal pathway MSNs. In DYT3, severe degeneration of striosomal MSNs that possess D1-receptors is found in the early disease phase when dystonia symptoms occur (dystonia phase). M, matrix compartment; S, striosome compartment; GPe, globus pallidus externa; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; GPi, globus pallidus internus; SNr, substantia nigra pars reticulata.

Subjects and methods

This randomized clinical trial was approved by the Institutional Ethics Committee. The study was registered with the International Committee of Medical Journal Editors recognized registry, the UMIN Clinical Trials Registry (number: UMIN00027430; date of permission: May 21, 2017).

Subjects

This study enrolled 21 patients with blepharospasms (six men and fifteen women) with an age range of 51–79 years (mean age average, 68.7 ± 7.8 years). Blepharospasm was diagnosed according to the criteria of Albanese et al. (2). Blepharospasm are characterized by focal involuntary contractions that interfere with physiological opening or closing of the eyelids, and those are caused by dystonic contractions of the orbicularis oculi often accompanied by contractions of the procerus and corrugator muscles. Onset is usually insidious, with eye irritation or dryness followed by excessive blinking, especially in bright light. All participants were examined by a single qualified neurologist, movement disorder specialist (S.M.) who performed general physical and neurological examinations to confirm the absence of neurological abnormalities other than blepharospasm. We carefully excluded the patients with dementia or apparent psychiatric disorders and/or those who taking medications that might affect dopamine signaling.

Brain magnetic resonance imaging and laboratory and genetic tests were performed to exclude hereditary and secondary dystonia. For genetic tests, we screened for pathogenic variants in known dystonia genes using whole-exome sequencing (OMIM Phenotypic Series PS128100).

All patients who had received BTX type A (BTX-A) treatment were instructed to undergo a 3-month washout period from the last BTX-A injection until the start of this clinical trial. In all of them, the medications except for L-DOPA and CPZ were unchanged from 3 months prior to the start of the clinical trial to the end of it. Video analyses were performed before and after the drug challenge tests (Figure 2).

Drugs

We used Dopacol tablets L50^{TM} (DOPACOL) (50 mg of L-DOPA plus 5 mg of carbidopa; Nichi-Iko Pharmaceutical Co., Ltd. Toyama, Japan) and Wintermin fine granules (10%; 180 mg

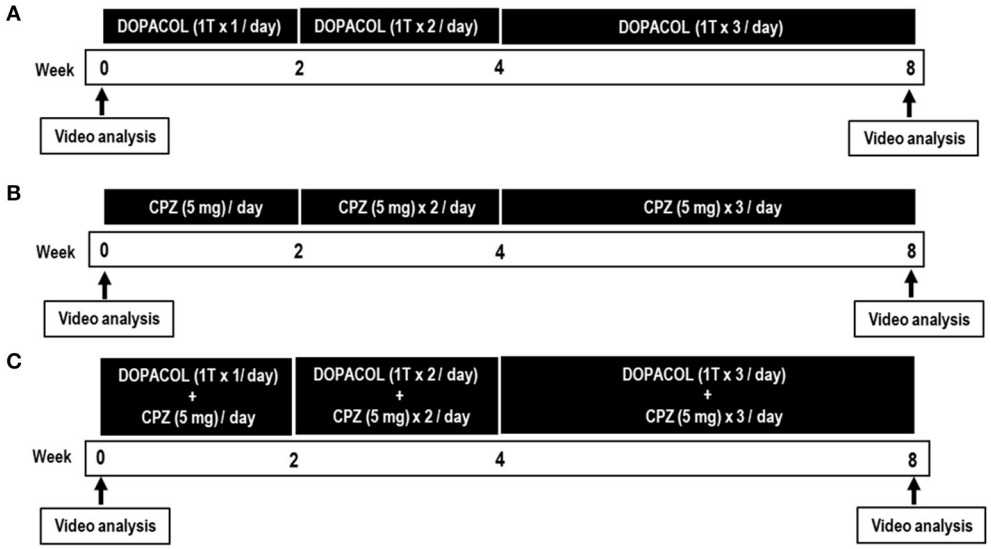

FIGURE 2
Timetable for the drug challenge tests with Dopacol tablets L50^{TM} (DOPACOL) (**A**), chlorpromazine (CPZ) (**B**), and DOPACOL + CPZ (**C**). T, tablet. Clinical evaluations and video recordings were performed 1 day before (pre-treatment) and 8 weeks after (post-treatment) the initial administration of the drugs.

of chlorpromazine phenolphthalinate per gram; Shionogi & Co., Ltd. Osaka, Japan).

Patient sorting and drug administration

There were 415 patients with blepharospasm who attended our hospital by the end of 2021. All of them had received BTX-A injection into the orbicularis oculi muscles as a first-line treatment, but some of them were refractory. Several studies have reported that some patients have not responded to BTX-A therapy (29–32), categorized as primary non-responders (33). In one study, 9.1 and 7.5% of patients were thought to have "primary resistance" and "secondary resistance," respectively (30). Patients who poorly responded to BTX-A treatment were randomly assigned to the following three groups (L-DOPA, CPZ, and L-DOPA + CPZ groups) in the order of consent. In a double-blind fashion, participants and evaluators were not informed of the identification of each group.

Although we happened to have had unequal sex distribution among the groups after randomized patient sorting (Table 1), it is well documented that blepharospasm shows a female-to-male preponderance in prevalence, with a reported male-to-female ratio between 1:2 and 1:8 (4, 34, 35).

L-DOPA group

This group included seven patients with blepharospasms (three men and four women) who ingested DOPACOL alone (Figure 2A, Table 1). Their age range was 51–79 years (age average, 66.0 ± 10.1 years), and their mean disease duration was 10.7 ± 9.5 years. We prescribed DOPACOL (one tablet per day) for the first 2 weeks, DOPACOL (one tablet × 2/day) for the next 2 weeks, and DOPACOL (one tablet × 3/day) for the last 4 weeks.

CPZ group

This group included seven patients with blepharospasm (one man and six women) who ingested CPZ alone (Figure 2B, Table 1). Their age range was 60–72 years (age average, 66.4 ± 3.9 years), and their mean disease duration was 8.4 ± 5.9 years. We prescribed CPZ (5 mg/day) for the first 2 weeks, CPZ (5 mg × 2/day) for the next 2 weeks, and CPZ (5 mg × 3/day) for the last 4 weeks.

L-DOPA + CPZ group

This group included seven patients with blepharospasms (two men and five women) who ingested both DOPACOL and CPZ (Figure 2C, Table 1). Their age range was 66–78 years (age average, 73.5 ± 5.9 years), and their mean disease duration was 8.0 ± 7.6 years. We prescribed DOPACOL (one tablet/day) with CPZ (5 mg/day) for the first 2 weeks, DOPACOL (one tablet × 2/day) with CPZ (5 mg × 2/day) for the next 2 weeks, and DOPACOL (one tablet × 3/day) with CPZ (5 mg × 3/day) for the last 4 weeks.

TABLE 1 Assessments of blepharospasm symptoms by VAS, BSDI, mVAS and JRS.

Group	Total number (female)	Age (years)	Disease duration (years)	VAS		BSDI		mVAS		JRS	
				Before	After	Before	After	Before	After	Before	After
LDOPA	$n = 7$ (4)	66.0 ± 10.1	10.7 ± 9.5	63.4 ± 18.4	74.3 ± 22.8	11.6 ± 4.0	12.3 ± 3.7	141.3 ± 8.4	178.8 ± 24.3**	4.8 ± 1.3	5.1 ± 1.8
CPZ	$n = 7$ (6)	66.4 ± 3.9	8.4 ± 5.9	57.3 ± 16.1	57.6 ± 23.0	11.3 ± 4.2	10.7 ± 4.1	167.4 ± 20.9	175.4 ± 33.7	4.7 ± 1.5	4.7 ± 1.3
LDOPA + CPZ	$n = 7$ (5)	73.5 ± 5.9	8.0 ± 7.6	67.1 ± 14.6	44.8 ± 27.5*	15.1 ± 6.6	10.6 ± 6.7**	148.0 ± 17.4	116.5 ± 14.5**	5.9 ± 2.2	3.0 ± 2.3**

The severity of blepharospasm was evaluated by VAS, BSDI, mVAS and JRS before and after the drug administration in each group.
*P < 0.05, ** P < 0.01 (Wilcoxon signed-rank test) as compared to before the treatment.
VAS; visual analog scale, BSDI; blepharospasm disability index, mVAS; modified visual analog scale, JRS; Jankovic rating score, LDOPA; levodopa carbidopa hydrate, CPZ; chlorpromazine phenolphthalinate.

Clinical assessments and measures

As shown in Figure 2, clinical evaluations and video recordings were performed 1 day before (pre-treatment) and 8 weeks after (post-treatment) the initial administration of the drugs. The severity of blepharospasm was evaluated using the Visual Analog Scale (VAS) (36), Blepharospasm Disability Index (BSDI) (37), modified VAS (mVAS) (38), and Jankovic Rating Scale (JRS) (37, 39). The VAS and BSDI were used for subjective signs, and the mVAS and JRS were used for objective signs.

Pre-treatment period symptom severities and participant backgrounds

Comparison of gender, age and disease duration at the pre-treatment period revealed no significant group differences among three treatment groups ($P > 0.05$, Kruskal–Wallis test).

Comparison of subjective (VAS and BSDI) and objective (mVAS and JRS) measures at the pre-treatment period revealed significant group differences only in mVAS ($P < 0.05$, Kruskal–Wallis test). Therefor we performed Mann–Whitney U-test on mVAS between each two groups, and it showed a significant difference between "LDOPA" and "CPZ" groups ($P < 0.05$), but neither between "LDOPA" and "LDOPA + CPZ" groups ($P > 0.05$) nor between "CPZ" and "LDOPA + CPZ" groups ($P > 0.05$). Thus, no apparent differences were found between the "LDOPA + CPZ" group and the other two groups. This indicates that there is no problem in determining the therapeutic efficacy in "LDOPA + CPZ" group.

Statistical analyses

All values are expressed as mean ± SD. Statistical significance was evaluated using the non-parametric methods that include Wilcoxon signed-rank, Kruskal–Wallis, and Mann-Whitney U-tests. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS statistical software (version 11.0; IMB Corp., Armonk, NY, USA).

Results

In the L-DOPA group (Figure 3; top), symptom severity was significantly increased after the drug trial, as determined by the mVAS ($P < 0.05$, $r = 0.59$), but not by the VAS, BSDI, and JRS (Table 1). In the CPZ group (Figure 3; middle), there was no apparent change in symptom severity after the drug trial, as determined by the VAS, BSDI, mVAS, and JRS (Table 1). In the L-DOPA+CPZ group (Figure 3; bottom), symptom severity was significantly decreased by administration of L-DOPA with CPZ in all subjective and objective signs, as determined by the VAS ($P < 0.05$, $r = 0.53$), BSDI ($P < 0.05$, $r = 0.64$), mVAS ($P < 0.05$, $r = 0.59$), and JRS ($P < 0.05$, $r = 0.64$) (Table 1).

No apparent neuropsychiatric and neurobehavioral adverse effects were found in the L-DOPA, CPZ, and L-DOPA + CPZ groups and no patients dropped out during the drug challenge tests. Thus, the dual use of DOPACOL (one tablet × 3/day) and CPZ (5 mg × 3/day), but not the administration of DOPACOL (one tablet × 3/day) alone or CPZ (5 mg × 3/day) alone, can give rise to a therapeutic effect on blepharospasm (for a reference see Supplementary Video 1).

Discussion

The present study showed that the symptoms of blepharospasm, a type of focal dystonia, could be alleviated by dual dopaminergic therapy using both L-DOPA and CPZ, with dosages lower than the usual in clinical practice. In this study, we used CPZ phenolphthalinate (15 mg/day) and L-DOPA (150 mg/day) with carbidopa (15 mg/day). In contrast, the usual dosage of CPZ in adults is 30–100 mg/day, and, for psychiatric use, 50–450 mg/day (40, 41), while the standard maintenance dose of L-DOPA with carbidopa for advanced Parkinson's disease is ∼600–750 mg/day (42).

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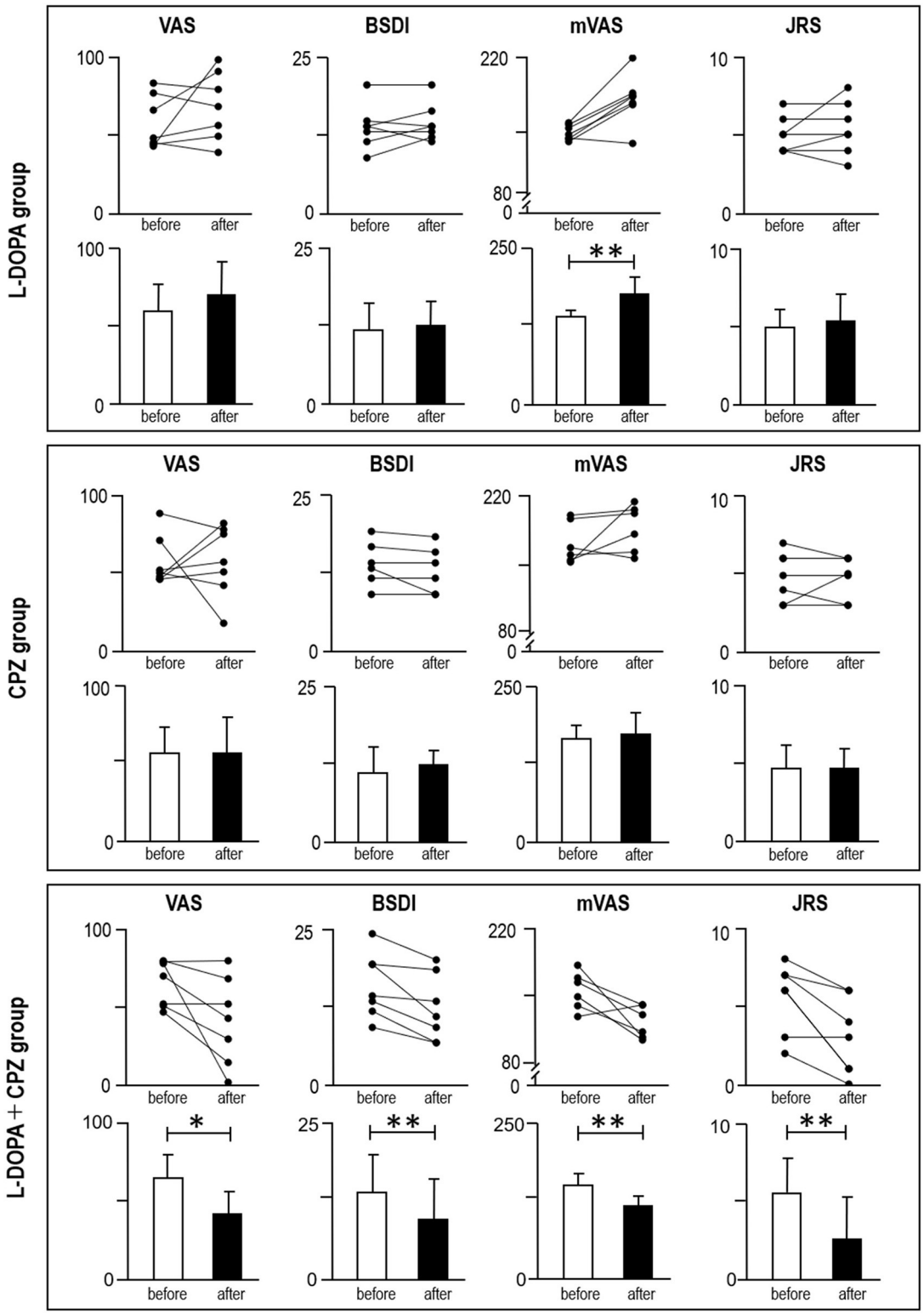

FIGURE 3
Measurements of blepharospasm severities before and after the drug challenge test. Symptom severities were determined by using visual analog scale (VAS), Blepharospasm Disability Index (BSDI), modified VAS (mVAS), and Jankovic Rating Scale (JRS). Line plots (upper graphs) and average plots (lower graphs) are shown in the "L-DOPA group ($n = 7$)" (top panel), "CPZ group ($n = 7$)" (middle panel), and "L-DOPA + CPZ group ($n = 7$)" (bottom panel). $^{*}P < 0.05$, $^{**}P < 0.01$ ("before" vs. "after", Wilcoxon signed-rank test).

Since L-DOPA is the prodrug of dopamine while CPZ is a D2-antagonist, our results suggest that dystonia symptoms could be attenuated through dopaminergic modulation, which induces an increase in striatal D1-signaling. Based on the evidence that D1Rs are highly concentrated in the striosome compartment in the "human" striatum (26), we also suggest that striosomal loss of D1 signaling may be important in the pathogenesis of dystonias (15, 16, 18, 21).

According to the classical D1-direct/D2-indirect pathway model (the so called "Matrix Model"; for reference, see Figure 1 "M, Matrix"), both matrix D1Rs and D2Rs are influenced by excessive dopamine signaling, causing abnormalities in individual firing rates and/or firing patterns in downstream structures (43–46). It is hypothesized that excessive dopamine signals could cause the activated D1-direct pathway and inhibited D2-indirect pathway to induce disinhibition and hyperexcitation of the thalamus and primary motor cortex, respectively, both of which result in hyperkinetic disorders such as dystonia (47, 48). Based on the classical matrix model, a D2-antagonist may improve dystonia symptoms via the D2-indirect pathway. However, the present study showed that the administration of CPZ (5 mg × 3/day) alone had no effect on blepharospasm symptoms. This is likely because the dose of CPZ used here was not high enough to affect dystonia symptoms.

One may say that even with the low dosage used here, administration of CPZ has a potential risk of causing tardive dystonia due to its D2-antagonistic action (49, 50). Because L-DOPA is a prodrug for dopamine that acts as both a D1 and D2 agonist (27), we consider that in dual therapy with L-DOPA and CPZ, simultaneous administration of L-DOPA can also dampen the D2-antagonism caused by CPZ and reduce the risk of tardive dystonia.

In conclusion, dual dopaminergic therapy with L-DOPA and CPZ can exert a therapeutic effect on blepharospasm, which is a focal dystonia. Our results suggest that dopaminergic modulation inducing an increase in striatal D1-signaling may attenuate dystonia symptoms, which is in accordance with the hypothesis that a loss of D1-signaling in the striosome compartment may underlie dystonia. Since the present study had a relatively small sample size, independent replications with a larger sample size may be warranted. It would be necessary to determine the optimal dosages for the most effective treatment of blepharospasm, because we have done this first clinical trial with relatively low doses of "L-DOPA and CPZ." It is also necessary to determine if the dual dopaminergic therapy used here could give rise to long-term and sustained benefits in patients with dystonias. It is currently under investigation to assess its therapeutic effects on the various types of focal dystonias (e.g. cervical dystonia, writer's cramp and other occupational dystonias), and the other types of idiopathic and/or secondary dystonias of which involves segmental or generalized body parts.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This randomized clinical trial was approved by the Institutional Ethics Committee of the Osaka Neurological Institute. The study was registered with the International Committee of Medical Journal Editors recognized registry, the UMIN Clinical Trials Registry (number: UMIN00027430). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SM: research project—conception, organization, and execution, statistical analysis—design, execution, and review and critique, and manuscript preparation—writing of the first draft. HK: research project—organization and execution. HS, RK, and SG: research project—conception, statistical analysis—design, execution, and review and critique, and manuscript preparation—review and critique. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.922333/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Therapeutic effects of pharmacotherapy with Dopacol tablets L50^{TM} (one tablet × 3/day) and chlorpromazine (5 mg × 3/day) on dystonia symptoms in a patient with blepharospasm.

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