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The Role of Nucleo-CMP as an Adjuvant Agent in the Treatment of Facial Palsy

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ABSTRACT

Background: *Nucleo cytidine-monophosphate (CMP) is a recently developed nootropic that has been used in various neuromuscular disorders.* ***Objective:*** *To investigate the role of nucleo-CMP containing regimen in the management of facial palsy as compared with conventional medicinal treatment regimens that include corticosteroids and/or antivirals. Thirty-five patients suffering from facial palsy (Grades 3-5) were given nucleo-CMP + corticosteroids + antivirals and monitored for three months. The results were compared with age and facial nerve grading score matched control group that was treated with the conventional regimen (corticosteroids + antivirals).* ***Results:*** *After taking the prescribed course of nucleo-CMP containing regimen, 34 out of 35 (97.1%) of patients made a complete (Grade 1) recovery within 40-120 days without any significant side effects). This response rate was significantly higher than the control group in which 30 out of 35 (85.71%) made a complete recovery (P=0.0023).* ***Conclusion:*** *These results suggest that nucleo-CMP is a promising new therapeutic agent that can be added to the conventionally prescribed regimens. These results warrant a randomized controlled clinical trial to re-evaluate the outcome and to optimize the use of nucleo-CMP as an adjuvant or as the primary prescribed treatment in a variety of patient groups.*

Keywords: Facial palsy, Corticosteroids, Antivirals, Nootropic agents

INTRODUCTION

Facial palsy is a potentially devastating condition that arises from acute inflammation and edema of the facial nerve resulting in weakness to move the affected side of the face. Moreover, patients may suffer from excessive tears due to impairment of parasympathetic innervation, hyperacusis due to impairment of certain auditory component [1,2]. A wide variety of causes may lead to facial palsy including herpes simplex, Ramsay Hunt syndrome, human immunodeficiency virus (HIV), meningitis, Lyme disease, sarcoidosis, and Guillain-Barre syndrome. However, Bell's palsy, which is an idiopathic form of facial palsy, constitutes approximately 70% of the cases [3]. Chronic systemic conditions such as diabetes mellitus and hypertension are ascribed as risk factors for Bell's palsy [4].

The diagnosis of facial palsy is primarily clinical. Several systems were described for grading the severity of facial palsy. The most widely accepted system is the House-Brackmann Grading System (HBGS) (Table 1) due to its ease of use and relative simplicity [5].

The standard medical treatment regimen constitutes the use of corticosteroids to reduce inflammation and edema [1], antiviral agents (to address viral infections) [6], and sometimes antibiotics (e.g. in the event of Lyme disease). There is a good deal of supporting evidence for the effectiveness of corticosteroids in the management of facial palsy as was stated in 2012 guidelines from the American Academy of Neurology (AAN) [7].

The use of corticosteroids has some limitations. It may be not advised to prescribe them in patients with diabetes mellitus, or patients with osteopenia, pregnancy, morbid obesity, or previous history of steroid intolerance [7,8].

There is some variation regarding the type of corticosteroids being prescribed. In general, it is restricted to prednisolone, prednisone, hydrocortisone [7], and dexamethasone [9]. With regard to antivirals, the choice alternates between acyclovir, valaciclovir, and famciclovir [6]. Nootropics are rapidly expanding class of drugs that are under focus nowadays to be utilized in the management of various neuronal disorders. One of the recently developed nootropics

is nucleo cytidine-monophosphate (CMP), which is a drug related to the nucleotides analogues that have been shown to be effective for the treatment of diverse peripheral neurological disorders.

Nucleo-CMP contains uridine monophosphate, uridine diphosphate, and uridine triphosphate with cysteine monophosphate. Nucleotides have been prescribed for patients suffering from diabetic neuropathy and neuromuscular disorders [10-12]. Some *in vivo* studies have shown that nucleotides accelerate nerve [13], muscle regeneration following injury to the sciatic nerve [14] and inhibit the transmission of spinal pain. Moreover, they improve recovery after exhaustive exercise [15]. Recent studies have demonstrated that nucleotide drugs activate P2 nucleotide receptors, and therefore exhibit a significant antinociceptive effect in the management of acute and neuropathic pain [16]. Nucleo-CMP has been successfully used in the treatment of progressive spastic paraparesis and it is free of side effects, drug interactions, and can be used safely during pregnancy and lactation [12,17].

Overall, the prognosis of facial palsy is favorable and most of the cases (approximately 70%) recover spontaneously within 3 months without treatment [18]. Researches have shown that younger age shows a favorable prognosis [19-21], while gender does not play any significant role [22].

The treatment of facial palsy is still controversial [23]. The main goals of treatment are to restore facial nerve function and decrease neuronal damage. The use of corticosteroids and antivirals is directed to relieve neuronal inflammation and viral involvement respectively. Nucleo-CMP could be a promising new add-on therapeutic agent to accelerate and restore facial nerve function. Thus, we proceeded with the objective: To investigate the role of nucleo-CMP containing regimen in the management of facial palsy as compared to the conventional medicinal treatment regimens that include corticosteroids and/or antivirals.

MATERIALS AND METHODS

This is a clinical pilot study performed in patients with facial paralysis who were attending a private neurology clinic during January 2016 to June 2016. This study was approved by the scientific committee in Al-Kindy College of Medicine. The study is in in accordance with the Helsinki Declaration of 1975 (revised in 2013). The eligibility criteria for this study included: patients presented with unilateral facial palsy, any age, and both genders. Patients were excluded if they have passed the 1st 72 h after onset of facial palsy, have recurrent facial nerve palsy, a central nervous system disease, traumatic facial nerve injury, pregnancy, metabolic disease, cancer, and psychiatric condition. The diagnosis of facial palsy was a clinical diagnosis done by a neurology specialist. After taking a thorough history and performing clinical examination, the facial palsy cases were graded according to the HBGS grading system (Table 1). Since the HBGS is the most widely grading system used in literature, we implemented it for comparing the response to nucleo-CMP with other modalities of treatment. Then, patients were interviewed, and a discussion was held about the case, medication, effect, and possible side effects. Then, an informed written consent was taken from them prior to the commencement of the study. Patients were divided into two groups that were age and facial nerve grading score matched. Nucleo-CMP treated group and a control group.

Table 1 House-Brackmann grading system

Type of dysfunction	Description
I. Normal	Normal facial function in all areas.
II. Mild dysfunction	Slight weakness noticeable on close inspection. No synkinesis, contracture, or hemifacial spasm. Normal symmetry and tone at rest. Moderate to good forehead function. Complete eye closure with minimal effort. Slight asymmetry of mouth.
III. Moderate dysfunction	Obvious, but not disfiguring difference between the sides. Noticeable, but not severe, synkinesis, contracture, or hemifacial spasm. Normal symmetry and tone at rest. Slight to moderate movement of forehead. Complete but asymmetric eye closure with effort. Slightly weak mouth movements with maximum effort.
IV. Moderately severe dysfunction	Obvious weakness or disfiguring asymmetry. Normal symmetry and tone at rest. No forehead movement. Incomplete eye closure. Asymmetry of mouth with maximum effort.
V. Severe dysfunction	Only barely perceptible motion. Asymmetry at rest. No forehead movement. Incomplete eye closure with only slight movement of lid with maximal effort. Slight movement of corner of mouth.
VI. Total paralysis	No movement.

Patients of Nucleo-CMP treated group were prescribed nucleo-CMP in doses of 10 mg/day (2 capsules/day, NUCLEO-CMP FORTE® manufactured by Ferrer, Barcelona, Spain) for three months with other drugs (which are routinely used): Acyclovir (ZOVIRAX® manufactured by GlaxoSmithKline, UK) 200 mg tab for children and 400 mg tab for adults 5x per day for the first 10 d only. Dexamethasone I.M. (24 mg) (Dexamethasone Sodium Phosphate® injection solution manufactured by Fresenius Kabi, USA) divided into 3 doses given every other day. Then, they continued the course of nucleo-CMP alone (on the same dose) for 3 months. Patients were followed-up every 2 weeks by the same neurology specialist.

The control group was treated with dexamethasone and acyclovir only (using the same previously mentioned doses) and followed up for the same duration.

Comparisons were made using percentages. Chi-Square test was used to measure statistical significance for age groups and recovery response implementing $^{*}P<0.05$ as significance level by using Graph pad prism 5 software.

RESULTS

We recruited 80 patients suffering from acute facial palsy. Ten patients failed to attend again for re-evaluation. Thus, we were left with 70 patients. Patients were equally divided to two groups containing 35 patients each: (Table 2). The patients mean age was 20.3 ± 7 years. There was no statistically significant difference between age groups. In each group (Table 3), 24 (68.6%) patients were initially Grade 4 (according to HBGS system), eight patients (22.9%) were initially Grade 5, and three patients (8.6%) were initially Grade 3. After taking the prescribed course of treatment mentioned above, 34 out of 35 (97.1%) patients of the nucleo-CMP treated group made a complete recovery (Grade 1 on HBGS system) within a duration of 40-120 days. One patient (2.9%) condition improved from grade 4 to grade 2. Regarding the control group, 30 out of 35 (85.71%) patients made a complete recovery.

Table 2 Patients demographics distribution by sex, age groups, and facial nerve grading score according to House-Brackmann grading system (HBGS). The control and the nucleo-CMP groups are matched according to age and facial nerve grading score

Sex	**Men N (%)**	**Women N (%)**
Control group	21 (60%)	14 (40%)
Nucleo-CMP group	19 (54.3%)	16 (45.7%)
Age	**Age group in years**	**N (%)**
	5-10	6 (17.14%)
	11-18	3 (8.57%)
	16-20	9 (25.71%)
	21-25	8 (22.85%)
	26-30	7 (20%)
	31-35	2 (5.71%)

Both groups, the control and the nucleo-CMP groups have shown a high statistical significance as compared with patients group before treatment P<0.0001. Interestingly, the nucleo-CMP treated group shows a high statistical significance P=0.0023 as compared with the control group.

Table 3 Facial palsy patients in terms of age and severity before and 3 months after the start of treatment as graded by House-Brackmann grading system. At the start, 80 patients were recruited. However, 10 of them failed to re-attend for follow-up. Thus, we were left with 70 patients. They were divided into two age and facial nerve grading score matched groups. Control group is treated with Acyclovir + Dexamethasone only. Nucleo-CMP was added to Acyclovir and Dexamethasone for the Nucleo-CMP treated group. Both groups were followed up for three months

Age groups	**HGBS Grades**	**Total (before treatment)**	**%**	**Control group**	**%**	**Nucleo-CMP treated group**	**%**
5-10 yrs	Grade I	-	-	6	100.00%	6	100.00%
	Grade II	-	-	-	-	-	-
	Grade III	4	33.30%	-	-	-	-
	Grade IV	8	66.70%	-	-	-	-
	Grade V	-	-	-	-	-	-

11-15 yrs	Grade I	-	-	3	100.00%	3	100.00%
	Grade II	-	-	-	-	-	-
	Grade III	-	-	-	-	-	-
	Grade IV	6	100.00%	-	-	-	-
	Grade V	-	-	-	-	-	-
16-20 yrs	Grade I	-	-	6	66.70%	8	88.90%
	Grade II	-	-	2	22.20%	1	11.10%
	Grade III	2	11.10%	1	11.10%	-	-
	Grade IV	10	55.60%	-	-	-	-
	Grade V	6	33.30%	-	-	-	-
21-25 yrs	Grade I	-	-	8	100.00%	8	100.00%
	Grade II	-	-	-	-	-	-
	Grade III	-	-	-	-	-	-
	Grade IV	10	62.50%	-	-	-	-
	Grade V	6	37.50%	-	-	-	-
26-30 yrs	Grade I	-	-	6	85.70%	7	100.00%
	Grade II	-	-	1	14.30%	-	-
	Grade III	-	-	-	-	-	-
	Grade IV	12	85.70%	-	-	-	-
	Grade V	2	14.30%	-	-	-	-
31-35 yrs	Grade I	-	-	1	-	-	-
	Grade II	-	-	1	50.00%	2	100.00%
	Grade III	-	-	-	-	-	-
	Grade IV	2	50.00%	-	-	-	-
	Grade V	2	50.00%	-	-	-	-
Total		70		35		35	

The patients (in both treated groups) did not complain of any significant side effects. Figure 1 shows images of selected patients before and after the treatment.

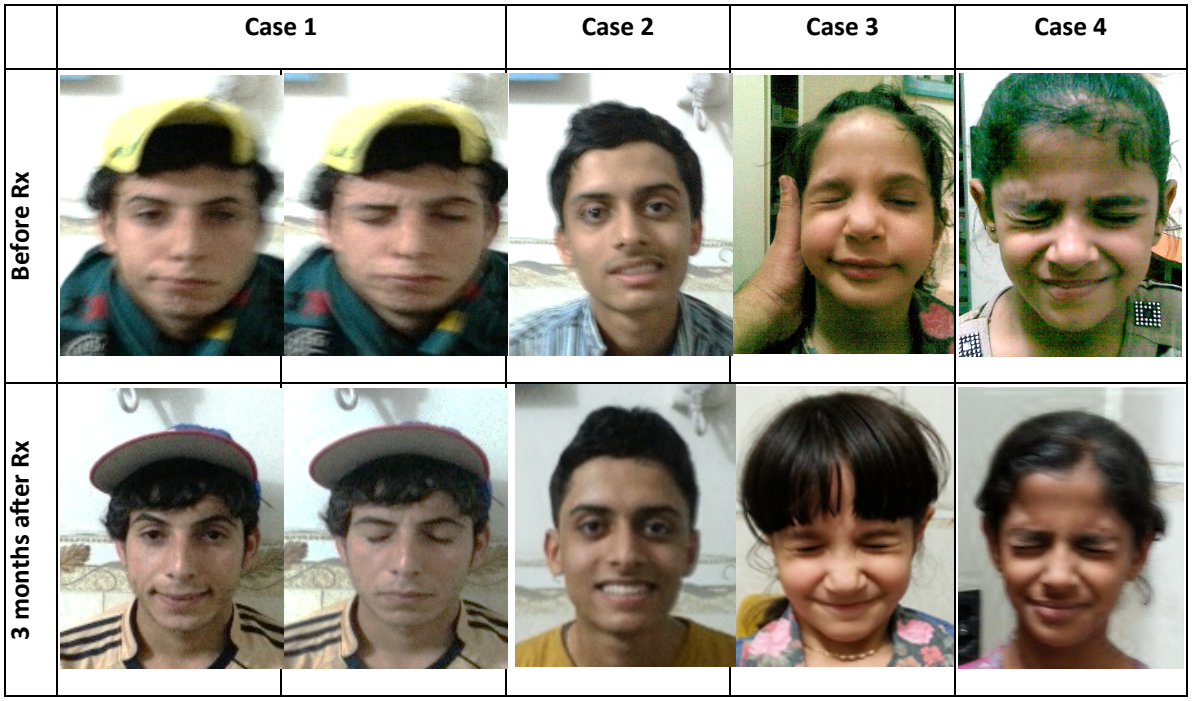

Figure 1 Pictures of selected cases before and after treatment with nucleo-CMP containing regimen.
In case 1, the patient, when first presented was asked to smile and then to close eyes forcefully which had shown weakness on the left side of face in the form of deviation of mouth to right (normal) side and weakness in

closing the left eye (affected side). However, after the 3 months of nucleo-CMP containing treatment the patient was able to smile and close both eyes symmetrically with no mouth deviation. The patient in case 2 was asked to smile which had shown weakness and deviation of mouth to the left (normal) side. 3 months post treatment he can smile normally with no mouth deviation. Cases 3 and 4 presented with poor left eye closure (affected side) and mouth deviation to right (normal) side on smile. After 3 months, the patient can symmetrically close eyes and there was no mouth deviation.

DISCUSSION

The results of our study clearly show the remarkable complete recovery of facial palsy patients after being treated with nucleo-CMP containing regimen as compared with the conventional regimens. Similarly, our study as compared with other studies implementing conventional regimens containing corticosteroids and/or antivirals shows a superior effective therapeutic role for nucleo-CMP. The systematic review [Antiviral treatment for Bell's palsy (idiopathic facial paralysis)] published by Cochrane Collaboration has analyzed 11 trials including 2883 participants. The patients were divided to several groups according to the regimens administered (corticosteroids + antivirals, corticosteroids alone, antivirals alone, and placebo alone). About 87% of patients have made complete recovery in response to corticosteroids + antivirals (which is 10.1% less than our result (97.1%)), while 81.2% of patients had complete recovery in response to corticosteroids alone. There was mild significant effect of using corticosteroids alone over using antivirals alone (RR 2.09, 95% CI 1.36 to 3.20). The treatment effect of placebo was significantly lower than that of antivirals plus corticosteroids (RR 0.56, 95% CI 0.41 to 0.76). Antivirals alone had a non-significant detrimental effect on the outcome compared with placebo (RR 1.10, 95% CI 0.87 to 1.40) [6]. Regarding adverse events on drug prescription, the review has shown adverse events developing in 10.8% of (corticosteroids alone patients) and 12.7% of (corticosteroids + antivirals patients). The good outcome after nucleo-CMP usage could be related to its mechanism of action by enhancing neuronal regeneration. In our study, no adverse effects of importance were encountered unlike Cochrane review where adverse events were reported (10.8% of (corticosteroids alone patients) and 12.7% of (corticosteroids + antivirals patients)). This may be due to the small sample size as compared with the previously mentioned review. In summary, a nucleo-CMP containing regimen is the optimal choice for treating facial palsy when compared to the previously mentioned regimens.

CONCLUSION

This is the first clinical study to investigate the possible therapeutic role of nucleo-CMP in the management of facial palsy. We provided for the first time the clinical evidence for the benefit of using nucleo-CMP as an add-on therapy. Thus, the results of this study could pave the way for the recommendation of using nucleo-CMP as an add-on therapeutic agent in the conventional regimens prescribed for the management of facial palsy. Further randomized trials on various patient groups (such as pregnant or lactating ladies) are required to further re-evaluate and optimize nucleo-CMP containing regimens. Moreover, such trials are vital to investigate the possibility of using nucleo-CMP alone when the use of corticosteroids or antivirals may be unsuitable or unsafe since nucleo-CMP is known to be free from side effects or adverse drug interactions.

DECLARATIONS

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Conflict of Interest

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

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