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Utility of high-dose clonidine in managing pediatric dystonia: A case series in a multi-ethnic Asian population

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Abstract

Background: Dystonia is a debilitating movement disorder. Clonidine, an alpha-2 agonist, is reported to be beneficial for pediatric dystonia. The use of high-dose clonidine remains poorly documented. We aimed to describe our experience with high-dose clonidine. *Methods:* Dystonia-Severity-Action-Plan (DSAP) is used to evaluate the severity of dystonia. *Results:* The clinical information of five children, seen at KK Hospital between 2019 and 2023, on high-dose clonidine were reviewed and reported. High-dose clonidine was effective in the management of severe exacerbations of dystonia, with an improvement in DSAP scoring. Clonidine may be administered enterally, intravenously, and through the transdermal route. The median dose reported was 2 mcg/kg/h, with doses up to 6 mcg/kg/h. Adverse effects reported were dose-dependent and include bradycardia, hypotension, sedation, and application site reaction.
Conclusion: High-dose clonidine is effective in improving severe dystonia in our multi-ethnic Asian population, and well tolerated. Our experience complements the existing data and suggest that high-dose clonidine can be considered in the management of pediatric dystonia and status dystonicus.

Keywords: Dystonia, clonidine, pediatric, neurology, pharmacy

INTRODUCTION

Dystonia, a complex neurological movement disorder, is characterised by involuntary, sustained, or intermittent muscle contractions, resulting in abnormal, repetitive movements or posturing.[1,2] Potential complications of dystonia include pain, loss of function, pressure sores, and physical deformities.[2] Acute worsening of dystonia may progress to status dystonicus, which is associated with high mortality, involving widespread muscular contractions, causing respiratory and metabolic complications.[3] Management of dystonia and status dystonicus in pediatrics remains challenging due to a lack of robust evidence.[3,4]

Clonidine is reported to be beneficial for the management of dystonia, and status dystonicus.[3-8] There is a paucity of information in the utility of clonidine in pediatric movement disorder, with most studies being limited to case series from the United Kingdom.[2,4,6] We aim to report our experience with the use of high-dose clonidine in our multi-ethnic Asian population.

METHODS

This study was approved by SingHealth-Centralised-Institutional-Review-Board. Informed consent was obtained from all patients, and/or caregivers. The patients were seen in KK Women's and Children's Hospital (KKH) between 2019 and 2023. Relevant patient clinical data were collected from electronic case-notes.

Dystonia-Severity-Action-Plan (DSAP) is an objective clinical tool to evaluate the severity of dystonia (Supplementary Table 1).[9] It is the only scale to quantify the clinical severity of dystonia for our cases.

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RESULTS

Clinical summary

The clinical information of the patients is summarised in Table 1.

Patient 1

Fifteen-year-old, 50 kg, Chinese girl was admitted to Children Intensive Care Unit (CICU) for persistent seizures and altered mental status. She was treated for infective meningitis, and febrile infection-related epilepsy syndrome (FIRES).

Table 1: Summary of clonidine use in patients on high-dose clonidine

Patient	**1**	**2**	**3**	**4**	**5**
Age (year-old), gender	15, female	4, female	4, female	1, female	8, female
Weight (kg)	50	20	21	8	12
Ethnicity	Chinese	Chinese	Malay	Chinese	Malay
Diagnosis	Febrile infection-related epilepsy syndrome	Sepsis with cardiorespiratory collapse and multi-organ dysfunction	Intracranial high-grade sarcoma	WDR73 mutation associated neuro-developmental disorder	Epileptic encephalopathy
Clinical features	Dystonia, myoclonus	Dystonia, spasticity	Dystonia, spasticity	Dystonia, microcephaly, global developmental delay, optic atrophy	Dystonia, spasticity, global developmental delay
Care location	Intensive Care Unit	Intensive Care Unit	Intensive Care Unit	High-Dependency Unit	Outpatient
Maximum dose of clonidine (mcg/day)	7000	2900	1000	250	300
Maximum dose of clonidine (mcg/kg/h)	5.9	6.0	2.0	1.3	1.1
DSAP-grade (Initial)	4	3	4	4	2
DSAP-grade (Final/ discharge)	1	1	1	1	1
Route of clonidine received	Intravenous oral transdermal	Intravenous transdermal	Intravenous transdermal	Intravenous oral transdermal	Oral transdermal
Adverse effects	Bradycardia hypotension rashes sedation	Bradycardia hypotension rashes sedation	Bradycardia sedation	Bradycardia hypotension	Sedation skin hyper-pigmentation

DSAP: Dystonia-Severity-Action-Plan

The patient developed extensor dystonic posturing and repetitive, non-epileptic myoclonus affecting her shoulders on day 10 of illness (DSAP Grade 4). Clonidine intravenous infusion was started, escalated from 2 mcg/kg/h (2400 mcg/day) to 5.9 mcg/kg/h (7000 mcg/day). The involuntary muscle twitching and dystonic posturing improved (DSAP Grade 2). Clonidine was tapered on day 25 of illness over five days, to 1 mcg/kg/h (1200 mcg/day) and converted to transdermal clonidine. Sedation, transient hypotension, sinus bradycardia (with intravenous clonidine) and rashes (with transdermal clonidine) were reported and managed. The patient was discharged (DSAP Grade 1) with transdermal clonidine and baclofen (15 mg TDS) for her tone management. (Figure 1)

Patient 2

A 4-year-old, 20kg, Chinese girl was admitted to CICU for severe gastrointestinal sepsis with cardiorespiratory collapse and multi-organ dysfunction. She was in persistent vegetative state and started on clonidine intravenous infusion (0.5 mcg/kg/h; 200 mcg/day) for sedation. The patient developed bilateral ankle clonus, significant lower limb spasticity and dystonia (DSAP Grade 3). Due to her coagulopathic state, rectal and intramuscular medication administration route were deemed unsuitable. The dose of intravenous clonidine was increased to 6 mcg/kg/h (2900 mcg/day) by day 32 of illness, with improvement in her muscle tone (DSAP Grade 2). Transient hypotensive episodes were reported. Intravenous clonidine (6 mcg/kg/h; 2900 mcg/day) was converted to transdermal route (5.1 mcg/kg/h; 2100 mcg/day) over a month when the patient was clinically stable. Adverse effects attributed to clonidine includes bradycardia, hypotension, and sedation. Gabapentin was started on day 123 of illness, and gradually optimised to 300mg TDS. She was discharged well on day 134 of illness with transdermal clonidine, and gabapentin. The dose of clonidine was weaned off over the next 12 months, with good control of her muscle tone (DSAP Grade 1). (Patient 2)

Patient 3

A 4-year-old, 21kg, Malay girl, with a background of intracranial high-grade sarcoma, was electively admitted for tumor resection. The patient was started on regular intravenous clonidine (0.15 mcg/kg/h; 75 mcg/day) for sedation and analgesia in CICU. The patient developed mixed spasticity and dystonia. The intermittent dystonia gradually worsened to persistent dystonic spasms, requiring rescue lorazepam (DSAP Grade 4). Regular clonidine was increased on day 46 of admission (0.48 mcg/kg/h; 240 mcg/day) and converted to continuous infusion, with dosage ranging from 1 to 2 mcg/kg/h (500 mcg/day to 1000 mcg/day). Improvement of dystonia was reported (DSAP Grade 2). Clonidine was weaned over four days from 2 mcg/kg/h (1000 mcg/day) to 1.3 mcg/kg/h (650 mcg/day) and converted to transdermal clonidine (1.2 mcg/kg/h; 600 mcg/day). Transient bradycardia was documented with high-dose clonidine, which improved without intervention. No hypotension, or application site reaction was

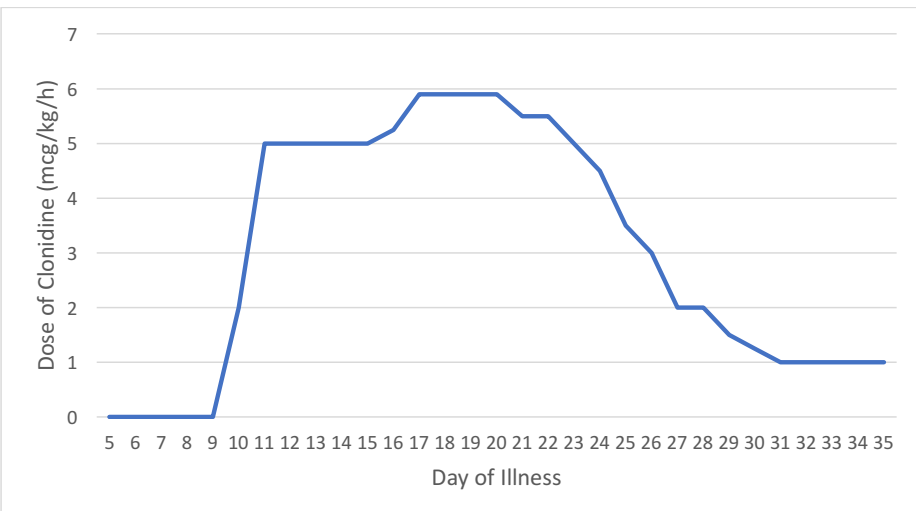

Figure 1. Dose of clonidine versus day of illness for Patient 1.

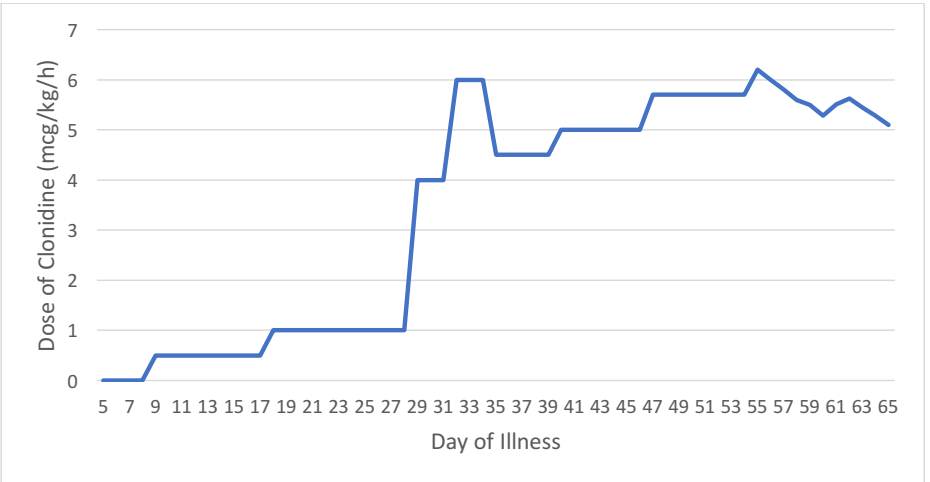

Figure 2. Dose of clonidine versus day of illness for Patient 2.

reported during hospitalisation. Baclofen was subsequently started, and optimised. The patient was discharged with baclofen (2.5mg TDS), and transdermal clonidine (DSAP Grade 1). (Figure 3)

Patient 4

A 1-year-old, 8kg, female Chinese patient with microcephaly, global developmental impairment, early-onset generalised dystonia and optic atrophy (associated with WDR73 mutation), was admitted for status dystonicus, and rhabdomyolysis (DSAP Grade 4). Laboratory investigations showed elevated serum potassium (5.7 mmol/L) and creatine kinase (1983 U/L). Rescue lorazepam was administered for emergency management. Her regular Madopar (levodopa/benserazide) was continued (10mg levodopa BD), and her clonidine regimen was escalated (0.31 mcg/kg/h; 60 mcg/day).

The intrusive dystonic episodes documented were of back arching with flexion of upper limbs, and oculogyric crisis. Her intravenous clonidine was escalated further (1.3 mcg/kg/h; 250 mcg/day). Bradycardia and hypotensive episodes were documented after clonidine was served, which limited the dose of clonidine. Chloral hydrate was also started to facilitate sleep.

No dystonic episodes reported on day four of admission (DSAP Grade 2). She was started on transdermal clonidine; the intravenous clonidine was converted to oral route and the dose was reduced. The patient required intermittent rescue doses of clonidine for breakthrough dystonia during the transition period but was otherwise clinically stable. Her serum potassium and

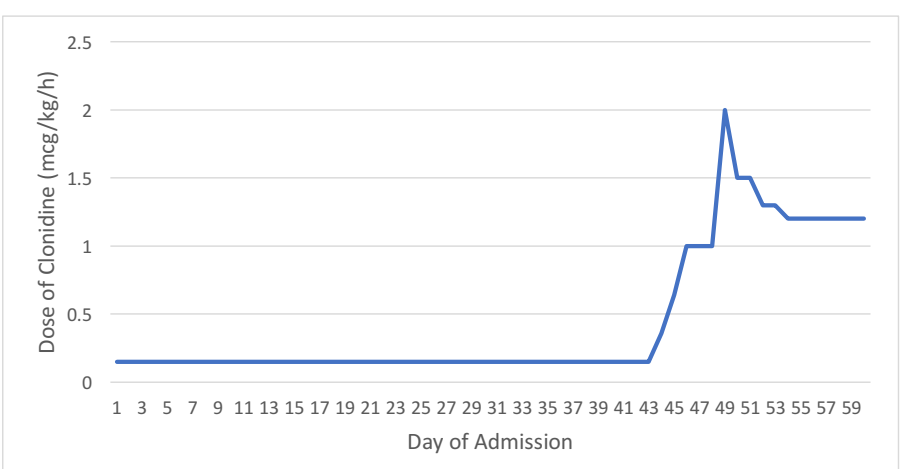

Figure 3. Dose of clonidine versus day of illness for Patient 3.

creatine kinase level were normal during discharge (DSAP Grade 1). The patient's Madopar dose was subsequently increased (20mg levodopa BD) and clonazepam was started. (Figure 4)

Patient 5

A 8-year-old, 13kg, Malay girl was followed-up at outpatient neurology clinic. She had a background of epileptic encephalopathy, movement disorder, and global developmental delay. Her movement phenotype comprised of generalised mixed spasticity, dystonia, and parkinsonian features. Concurrent medications include carbamazepine, clobazam, and topiramate for seizure control, benzhexol (3mg BD), and Madopar (50mg levodopa BD) for tone control.

The patient had intermittent segmental and truncal dystonia, as well as generalised spasticity, affecting her sitting posture (DSAP Grade 2). Oral clonidine (0.24 mcg/kg/h; 75 mcg/day) was started and gradually titrated over eight months to 300 mcg/day (0.96 mcg/kg/h), which was converted to transdermal clonidine on Day 814 after starting clonidine (DSAP Grade 1). The patient was also prescribed with oral rescue doses of clonidine. The patient tolerated her clonidine regimen well. Adverse effects reported includes sedation, and skin hyperpigmentation with transdermal clonidine. (Figure 5)

DISCUSSION

Efficacy and safety of clonidine

The median maximum dose reported was 2 mcg/kg/h, with doses ranging up to 6 mcg/kg/h. A clear temporal relationship was observed between the initiation/dose adjustment of high-dose clonidine and improvement in their DSAP scoring. Clonidine was the only anti-dystonic agent which was started or modified during which improvement in DSAP scoring was observed. Adverse effects attributed to high-dose clonidine included bradycardia (4/5), hypotension (3/5) and sedation (4/5). These reactions were transient, and dose-dependent, and improved without medical interventions. Transdermal clonidine was associated with application site reaction (3/5). These were managed by alternating patch application site and the use of topical corticosteroids.

Clonidine use in dystonia and status dystonicus

Clonidine, a central-acting, alpha-2 and imidazoline receptor agonist, inhibits sympathetic output from the central nervous system.[10,11] It is postulated to alleviate dystonic episodes by promoting sleep in patients with dystonia.[7]

The body of evidence supporting the usage of clonidine in dystonia remains underwhelming. An uncontrolled, retrospective analysis of 24 patients reported improvement in dystonia after clonidine was started, and clonidine was observed to be efficacious and well-tolerated[8]. Another case series at a single centre in United Kingdom describing the dosing regimen and tolerability of clonidine in the management of acute exacerbation of dystonia.[7] They concluded that the use of clonidine was effective in controlling dystonia and associated with minimal usage of respiratory support and sedatives.

Clonidine doses up to 9 mcg/kg/h were

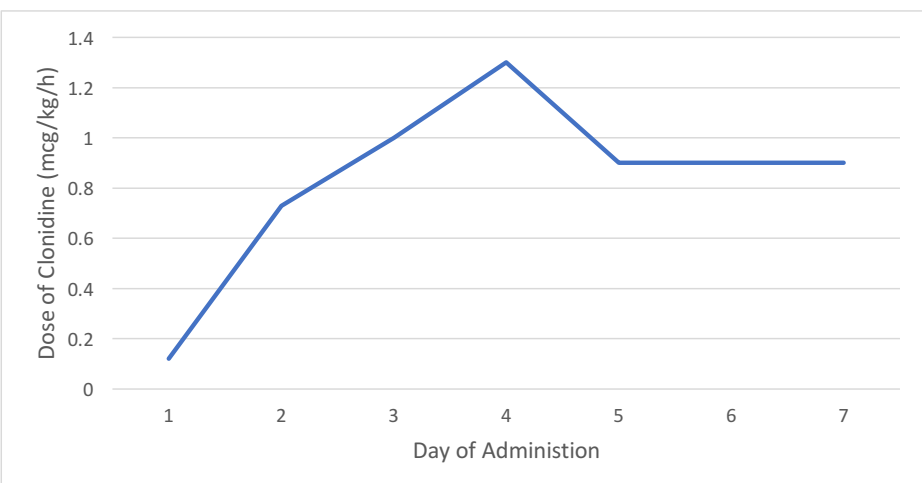

Figure 4. Dose of clonidine versus day of illness for Patient 4.

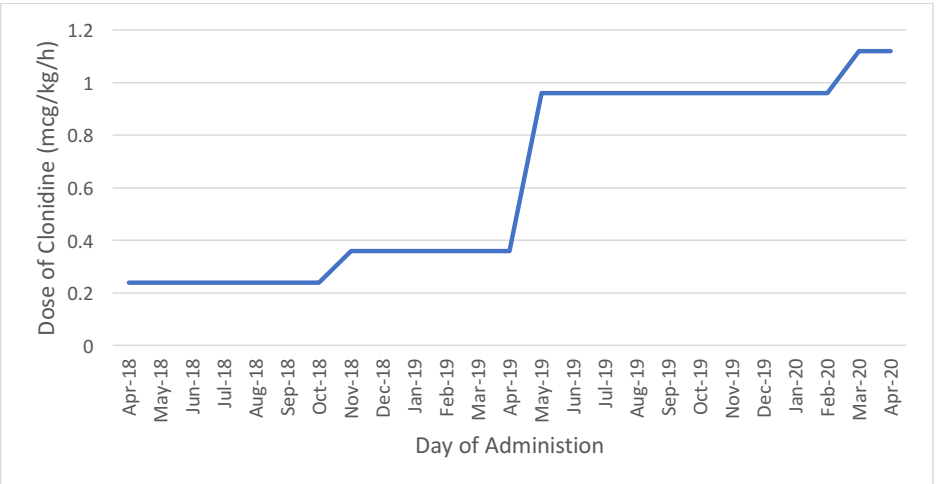

Figure 5. Dose of clonidine versus day of illness for Patient 5.

reported.[3,5,10,11] However, the absolute dose ceiling remains unclear. The first patient of this case series tolerated 7000 mcg/day with good control of her dystonia. Allen and colleague reported that doses up to 3000 mcg/day was required for a 70 kg patient.[3] In the context of accidental overdose of clonidine (<10 mg of clonidine), most patients recovered with supportive care.[12,13]

The main limitation of this study is its retrospective and observational design. The small sample size and a heterogeneous patient population limits the reliability and generalisability of our finding. While there is a strong temporal relationship between the use of high-dose clonidine and the improvement in dystonia control our five patients, it is challenging to establish a causal link between the two events.

This study is significant as this is the first report describing the use of high-dose clonidine for the management of pediatric dystonia in Asia. The phenotype of dystonia differs between different ethnicity groups, and this may affect the treatment approach and considerations in different region.[14] To our knowledge, this is the first report describing the use of high-dose clonidine for the management of pediatric dystonia in Asia.

Our experience with high-dose clonidine suggest that high-dose clonidine is generally well tolerated and reduced the severity of the dystonic episodes. While bradycardia and hypotension were reported in our patient population, they were transient and can be appropriately managed. High-dose clonidine was associated with improvement in DSAP grading and the benefit of therapy outweigh the risk.

Our data aims to complement current published reports on clonidine usage in a multi-ethnic Asian population and explore the dosing limit of clonidine further. High-dose clonidine may be considered as part of the treatment protocol in managing pediatric dystonia and status dystonicus. While our experience may not be applicable to the broader population, it may provide valuable insights in bridging the current knowledge gap.

In conclusion, high-dose clonidine has good effectiveness in improving severe dystonia in our multi-ethnic, Asian population. Pediatric movement disorder specialists in Asia may consider using high-dose clonidine for patients to manage intrusive dystonia. However, larger, and prospective pediatric study evaluating the use of high-dose clonidine is needed.

DISCLOSURE

Ethics: We confirmed that this study was approved by SingHealth Centralised Institutional Review Board (CIRB Reference: 2018/2916). Informed consent was obtained from all patients, and/or caregivers.

Financial support: None

Conflict of interest: None

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Supplementary Table 1: Dystonia Severity Assessment Plan (DSAP)

Grade	Description
1	The child sits comfortably and has regular periods of uninterrupted sleep. Child stable on medication.
2	The child is irritable and cannot settle. Dystonic posturing interferes with sitting activities. The child can only tolerate lying despite usual baseline medication.
3	Not able to tolerate lying and/ or unable to get to sleep or sleep disturbed. No evidence of metabolic decompensation, creatine kinase <1000 IU/L
4	Early multi-organ failure. Clinically as above with: Pyrexia (in absence of infection) Evidence of metabolic compromise (e.g. acidosis, elevated potassium, low calcium, evidence of rising creatinine and/ or urea) Evidence of myoglobinuria, creatine kinase >1000 IU/L
5	Immediately life threatening: As above with: Full metabolic decompensation Respiratory, cardiovascular, haematological (e.g. disseminated intravascular coagulation) or renal compromise requiring organ support. Requires intensive care

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