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Original article

Safety and efficacy of high-dose enteral, intravenous, and transdermal clonidine for the acute management of severe intractable childhood dystonia and status dystonicus: An illustrative case-series

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ABSTRACT

Objective: Acute dystonia in children is distressing, painful and can progress to life-threatening status dystonicus. Typical management involves benzodiazepines which can result in respiratory depression requiring PICU admission. Clonidine is less respiratory-depressant, and by facilitating sleep, switches dystonia off. It can also be administered via enteral, continuous intravenous infusion, and transdermal slow release routes. We describe the dose range and safety profile of clonidine management in a case-series of children with severe acute exacerbation of dystonia in a tertiary hospital setting.

Methods: The management of 5 children (3 female, age range 8–14 years) suffering from an acute exacerbation of secondary dystonia requiring hospital admission at the Evelina London Children's Hospital was reviewed. The average and maximum dose of clonidine in mcg/kg/h and routes of administration were recorded for each day of hospital admission. Co-administration of any other medical treatments for dystonia and their route of administration were also recorded. Cardiovascular and respiratory clinical status were measured by recording the daily mean and maximum Paediatric Early Warning Scores (PEWS).

Results: Clonidine was administered via enteral, intravenous, and transdermal routes at a median dose of 2.5 mcg/kg/h (range 0.1–9 mcg/kg/h). Administration of high dose clonidine was associated with decreased use of benzodiazepines, morphine, and propofol: avoiding invasive respiratory support for ¾ cases during admission. Clonidine doses via all routes of administration did not correlate with poorer PEWS scores ($p = 0.839$). Both high dose intravenous and transdermal clonidine where found to be effective.

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Conclusions: High dose clonidine administered via different routes can be used in the acute management of severe exacerbations of dystonia. Its use in our cohort was not associated with significant cardio-respiratory depression even at doses as high as 9 mcg/kg/h.

1. Introduction

Dystonia is characterised by involuntary sustained or intermittent muscle contractions that cause abnormal, often repetitive movements, postures or both.[1,2]

Acute worsening of dystonia in children is very distressful, painful and can progress to a life-threatening episode of status dystonicus, most typically in adolescents with cerebral palsy, with a 10% mortality and a need for prolonged hospital admission.[3]

Status dystonicus may occur spontaneously or be triggered by several factors, such as infection, gut dysmotility, abrupt medication withdrawal, or disruption of Deep Brain Stimulation (DBS).[4] Some children are prone to recurrent episodes.[5]

The evidence-base for pharmacological management of acute dystonia is limited. Typical management strategies involve the administration of high dose benzodiazepines and opiates which can result in respiratory depression and necessitate admission to a Paediatric Intensive Care Unit (PICU).[6]

1.1. *Clonidine*

Clonidine is an α-2 receptor agonist and imidazoline receptor agonist. Clonidine is a centrally active antihypertensive agent, with a short half-life, and effective in the treatment of mild, moderate and severe hypertension, alone or in combination with other drugs.[7]

Use of clonidine has been previously reported in the older literature as useful in the acute management of neuroleptic-induced tardive dyskinesia in adults being managed for psychosis using doses of about 500 micrograms (mcg) per day.[8] Clonidine has also been found to be useful in the management of alcohol, opiate, and nicotine withdrawal syndromes and tic disorders in large randomized controlled studies using clonidine patches[9] and also tics with co-existing attention-deficit/hyperactivity disorder (ADHD).[10] Additionally clonidine has mild sedative effects, which is advantageous in the management of sleep disorders, especially in children with neurodevelopmental disorders[11] and more recently clonidine was reported as highly beneficial in the management of acute NMDA-receptor antibody-meditated encephalitis for the movement and neuropsychiatric symptoms[12]

Our experience with out-patient use of clonidine for the chronic management of childhood dystonia in the out-patient setting has recently been reported (Sayer EJPN epub 2017)[13] as a result of which we no longer perform an in-hospital test-dose procedure of 1 mcg/kg of oral clonidine followed by blood pressure measurement to exclude hypotension because no cases of hypotension were provoked.

Clonidine can be very beneficial in the management of acute worsening of dystonia as well as in established status dystonicus, although the exact mechanisms for these actions are not known, hypnotic and anxiolytic actions probably play an important role.

In comparison to benzodiazepines and opiates, clonidine is a less sedating alternative which causes little or no respiratory depression and can obviate the need for subsequent ventilator support.[6]

Clonidine can be administered via enteral, continuous intravenous (IV) infusion, and transdermal slow release routes.[9]

There is little experience of use of iv clonidine outside the PICU setting and no reports of clonidine for acute dystonia in childhood.

Here we report the use of high dose clonidine in the management of severe acute dystonia outside PICU in a case-series of 5 children. Importantly with one exception, ventilatory support was not required. We also report our experience with transdermal clonidine which reduces reliance on iv administration in the context of unreliable gut function.

2. Methods

The management of 5 children (3 female, age range 8–14 years) suffering from an acute exacerbation of secondary dystonia requiring hospital admission under the care of the Paediatric Complex Motor Disorders Service at the Evelina London Children's Hospital was retrospectively and prospectively reviewed.

Dystonia severity was measured, using the Dystonia Severity Action Plan (DSAP) grades 1–5.[14]

Grades 1–5 defined as:

Grade 1: Sitting comfortably
Grade 2: Unable to sit but able to sleep at night
Grade 3: Unable to sleep or sit comfortably
Grade 4: Metabolic decompensation, sweating, rhabdomyolysis, requires HDU
Grade 5: Status dystonicus & multi-organ failure, requires PICU

The DSAP grading (see Table 1 for details) has recently been used to describe approaches to the management of status dystonicus[15] can also be re-phrased as 'Dystonia Soon As Possible' to emphasize the underlying urgency to control dystonia and prevent inevitable progression to DSAP grades 4 and 5.

The daily dose of clonidine (in mcg/kg/h) and route of administration were recorded for each day of hospital