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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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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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What this paper adds?

Status dystonicus remains a complex multisystem disorder and usually involves a multidisciplinary approach.

Clonidine may provide a suitable alternative to benzodiazepines and opiate infusions in the management of childhood status dystonicus.

Clonidine doses of 0.5-3mcg/kg/hour (range 0.1- 9mcg/kg/hour) may be necessary to safely manage acute severe dystonia and in our experience does not result in severe hypotension or respiratory depression

Severe dystonia is effectively managed using the Dystonia Severity Assessment Plan (DSAP) scoring system which monitors worsening and improvement in dystonia based on meaningful function and comfort

Clonidine helps to restore sleep in dystonic children which in turn is crucial for breaking the vicious cycle of continuous muscular contraction of dystonia

Attention to the sleep patterns of children with dystonia and improving their often fragmented sleep forms the cornerstone of dystonia management

Key words

Clonidine

Status Dystonicus

Dystonia

Childhood

Safety

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 treatment 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/hr 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 2.5mcg/kg/hr (range 0.1 to 9 mcg/kg/hr). Administration of high dose clonidine was associated with decreased use of benzodiazepines, morphine, and propofol: avoiding invasive respiratory support for $\frac{3}{4}$ 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 were found to be effective.

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/hr.

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

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 day⁸. 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 patches⁹ 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 disorders¹¹ and more recently clonidine was reported as highly beneficial in the management of acute NMDA-receptor antibody-mediated encephalitis for the movement and neuropsychiatric symptoms¹²

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 1microgram/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 routes⁹.

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.

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 Movement Disorder Service at the Evelina London Children's Hospital was retrospectively and prospectively reviewed.

Dystonia severity was measured, using the Dystonia Severity Assessment 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 dystonicus¹⁵ 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/hr) and route 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 reviewed by recording the daily mean and maximum Paediatric Early Warning Scores (PEWS).

Results

The five cases are briefly presented.

Case1: A nine year old boy with dystonic cerebral palsy, one of twins, with Gross Motor Function Classification System (GMFCS)¹⁶ level 5 and Manual Abilities Classification System (MACS)¹⁶ level 5 Communication Function Classification System (CFCS)¹⁶ level V secondary to prematurity at 24 weeks gestation associated with haemorrhagic destruction of cerebellar hemispheres, sensorineural

deafness, developmental delay, learning difficulties, renal calculi and sleep problems. Feeding was via gastrostomy though he usually managed some oral feeds. He had been successfully managed for four years with bilateral globus pallidus internus (GPI) deep brain stimulation followed by unilateral cochlear implantation at 5 years of age (see Lin et al EJPN special edition 2016)¹⁷. He presented acutely with status dystonicus and rhabdomyolysis, DSAP level V, figure 1a, 10 days after Deep Brain Stimulation removal in November 2012 because of neurostimulator erosion associated with infra-clavicular neurostimulator pocket infection requiring high dose antibiotics. High dose IV clonidine, up to 9mcg/kg/hour, as high-dose benzodiazepines (midazolam, lorazepam, diazepam, and nitrazepam), propofol and morphine infusions were ineffective. Figure 1b shows optimization of the clonidine up to a brief maximum of 9micrograms/kg/hr which was rapidly weaned after re-implantation of the DBS system. Note the rise in the PEWS score in the first 3 weeks during the midazolam infusion. Despite the clonidine dose rising after initial DBS re-implantation, the PEWS is more stable than when on midazolam. The transdermal clonidine is introduced on day 48 because of ileus and several episodes of unexplained gastric mucosal bleeding for which no cause was found on endoscopy, building up to a steady transdermal dose of 2mcg/kg/hr of clonidine. Figure 1b shows the slow improvement in the DSAP score which demonstrates sitting consistently comfortably at 240-250days after initial admission. He was successfully discharged home 9 months after and remains on 900micrograms of transdermal clonidine in the form of 3 three-hundred microgram patches 4 years later: each patch lasting 7 days.

Case2:

An eleven year old girl with Pantothenate Kinases Associated Neurodegeneration (PKAN) with a positive PANK2-mutation presenting with severe sustained generalized dystonia, GMFCS level V, feeding via gastrostomy, was transferred for further management from another tertiary referral centre due to acute worsening dystonia. On admission, sleep and sitting out in a chair were severely disrupted (DSAP grade 3). Gradual escalation of clonidine up to 2.1mcg/kg/hr over 18 days was administered enterally for dystonia control (figure 2). Sleep improved by day 20 (DSAP Grade 2) and intermittent sitting out in her chair from day 16 (DSAP Grade 1). Deep Brain Stimulation was implanted as planned 3 months later.

Case3:

A seven year old girl with microcephaly, severe choreoathetoid movement disorder and profound developmental delay with no underlying diagnosis and GMFCS level V was admitted after Deep Brain stimulation surgery with severe hyperkinetic movements, worsening during an intercurrent respiratory infection. Escalation of oral clonidine up to 3.9mcg/kg/hour on day 15 resulted in a DSAP improvement from Grade 3 (unable to sleep) to DSAP Grade 1 on day 17 and also allowed weaning of nitrazepam and reduced the involuntary movements during the episode of infection. (figure 3)

Case4:

A fourteen year-old girl with early epileptic encephalopathy and choreoathetoid movement disorder, associated with GNAO1 mutation, GMFCS level IV presented to her local hospital with a severe dystonic-choreoathetoid crisis requiring admission to her Regional Paediatric Intensive Care Unit (PICU) for 5 weeks from which she was transferred to our unit for deep brain stimulation (DBS). Prior to transfer, management of the dystonic-choreoathetoid crisis was greatly helped by initiating

a high-dose clonidine IV infusion at 3.5micrograms/kg/hour. This was subsequently converted to enteral clonidine via nasogastric tube infusion. This clonidine infusion allowed comfortable lying in bed and sleeping at night but sitting out in her chair only resumed after bilateral globus pallidus internus (GPi) DBS followed by gradual mobilisation leading to gradual clonidine weaning to zero prior to transfer back to her local hospital (figure 4).

Case5:

A fourteen year old boy with dystonic-dyskinetic cerebral palsy and epilepsy, GMFCS Level V, severe sleep problems and jejunostomy feeding, presented in status dystonicus in July 2015, associated with septicaemia and ileus, after having bilateral hip surgery, requiring admission to PICU.

He was started on IV clonidine, which helped his symptoms to settle gradually.

There was a noticeable exacerbation of his dystonia during his treatment course, with increasing of DSAP score from 1 to 3, when the dose of clonidine was inadvertently reduced from 1mcg/kg/hour to 0.1mcg/kg/hour, followed by a quick response and clinical improvement once he was given the correct dose (figure 5).

The clonidine infusion reached a maximum rate of 2.7mcg/kg/hr and was switched to enteral administration, when gut mobility was restored (figure 5).

Relationship of PEWS, DSAP and Clonidine doses

A major clinical concern is the possibility of cardiovascular compromise relating to bradycardia and hypotension with clonidine use. Although a relative bradycardia during sleep was an almost invariable finding, the heart rate always increased with appropriate physiological variability during arousal or wakeful hours. The Paediatric Early Warning Score is designed to give nursing and medical teams early indication of deteriorating vital signs and possible need for escalation of life support (reference). In all 5 cases the PEWS varied with the underlying illness of the child but did not worsen with increasing doses of clonidine. In cases 2,3 and 5 the PEWS severity matched DSAP severity and improved as the clonidine increased. This is particularly seen in cases 3 and 5. In case 3, an intercurrent viral infection from day 9 to 13 resulted in worsening of the PEWS score to 4.5. The clonidine was then further increased over day 13-15 and the DSAP Grade 3 dropped to between down to Grade 1-2 on day 17. In case 5 an administrative error resulted in only 0.1mcg/kg/hr being administered instead of 1.0mcg/kg/hr leading to immediate rebound dystonia reflected in a high DSAP grade 3 and a PEWS of 3.5 which improved as soon as the correct infusion dose of 1.0mcg/kg/hr was restored.

Overall there was no significant correlation between worsening PEWS and clonidine dose (Spearman's rho 0.0494; p=0.7928) and no episodes of clinically significant hypotension, though as anticipated nursing staff did alert medical teams when bradycardia was recorded almost always during sleep and generally abolished by wakefulness.

Discussion

We present this illustrative case-series of 5 children, including 2 cases of cerebral palsy with acute status dystonicus refractory to conventional drug management. Clonidine was administered via

enteral, intravenous, and transdermal routes at a median dose of 2.5mcg/kg/hr (range 0.1 to 9 mcg/kg/hr) with benefit in reducing dystonia, restoring sleep and allowing a return to sitting comfortably.

An enteral dosage of 1-5mcg/kg/dose may be administered initially 8-hourly but if dystonia breaks through, this dose may need to be administered more frequently. In acute worsening dystonia in the hospital setting, typical doses of 0.5- 3mcg/kg/hour are usually very effective but we have had to use much higher doses up to 9mcg/kg/hour if necessary, and in our experience does not result in hypotension or respiratory depression. Clonidine can also be administered by continuous enteral infusion via NG tube or gastrostomy, by calculating the total daily dose and dividing by 24 hours to deliver.

Intravenous clonidine dosage:

Clonidine can be administered as IV Continuous infusion when enteral route is unsuitable owing to diarrhoea and vomiting, gut failure, or temporary loss of gastrostomy. Doses of 0.25-2.0 mcg/kg/hour are mainly used in daily PICU practise, but for severe dystonia, consideration of higher doses as tolerated may be required.

Transdermal slow release routes

Transdermal patches are another option of administering clonidine, especially in patients with gut failure and the need to establish long-term high dose of clonidine while avoiding the intravenous route of administration. This has recently been reported in a teenage boy with an end-stage leucodystrophy and severe dystonia receiving palliative care¹⁸.

Administration of high dose clonidine was associated with avoiding the use of respiratory depressant benzodiazepines, morphine, and propofol thus avoiding invasive respiratory support for 4/5 cases during admission.

The DSAP grade and clonidine in dystonia

In all cases the DSAP grade^{14,15} improved or did not deteriorate as clonidine was increased. The DSAP helps to measure the important clinical variables of well-being in dystonic children: the ability to sleep and sit comfortably as well as monitor dystonia worsening: sweating, dehydration, rhabdomyolysis (DSAP Grade 4) and Status Dystonicus (DSAP Grade 5) associated with multi-organ failure. The DSAP also monitors the gradual recovery from status dystonicus and allows parents and healthcare professionals to determine progress. Children may still experience difficult dystonic episodes but the quality of life is greatly enhanced if the child is able to sleep 6 or more hours a day and to sit out in a chair for 1-2 hours a day. The sleep-wake pattern can be usefully monitored during exacerbations and indeed during dystonic crises using a simple 24-hour sleep-wake chart that monitors sleep, wakefulness, comfort, dystonia and sitting out in a chair for each hour. This diary can be used as children are transferred to other units and at home and school.

Clonidine and PEWS

Clonidine doses via all routes of administration did not correlate with a worsening PEWS score suggesting no additional compromise of cardiovascular or respiratory function at even very high doses.

Clonidine and sleep bradycardia

A universal observation of children with dystonia who are on clonidine is the relative bradycardia during sleep. This phenomenon is not observed in the awake state, indicating the physiological nature of the bradycardia during sleep. Such a bradycardia is not an indication for withholding clonidine provided gentle stimulation of the child results in a rise in heart rate to demonstrate an arousal-dependent variability in heart rate.

Reducing un-necessary polypharmacy

However where possible, all unsuccessful antidystonic medication should be discontinued by gradual weaning to avoid polypharmacy and the risk of gut ileus.

Specific comment on side effects experienced on clonidine

Limitations of our report.

These case histories merely illustrate that the condition of severe dystonia is often difficult to manage and often require coordinated multidisciplinary collaboration. Safely relieving acute severe dystonia without inducing respiratory failure and minimising invasive methods of administration has been our chief goal, but this report is nevertheless limited by the small number of cases. Over several years, our dosage regimens have become bolder as we have come to accept that higher total daily doses of clonidine are required in the severely dystonic child while recognising that tapering these doses or adjusting them to achieve the best night-day or sleep-wake pattern requires active clinical judgement.

This work represents a parallel audit of clonidine use for dystonia in the out-patient clinic setting when smaller, and more slowly adjusted clonidine increments are made¹³.

Contact from colleagues within the UK and abroad suggested that a descriptive account of some representative cases was needed to establish how we use clonidine effectively and safely, rather than the word-of-mouth jungle telegraph approach to date.

It would be an extension to these initial case-history descriptions to collect more data with a wider clinical spectrum of cases on the precipitating factors leading to severe dystonia and status dystonicus and how to manage this effectively, preferably by early recognition and institution of a prophylactic plan. This has occurred informally in collaboration with our orthopaedic colleagues, anticipating worsening dystonia following planned surgery to hips and spine by instituting clonidine on admission for such surgery and early escalation as indicated postoperatively.

It is anticipated that new tools such as a parent/carer-held 'My Dystonia-Child' APP, based on the DSAP and other measures, could help to monitor the well-being of children with dystonia and provide us with a larger database that could help gather information on all forms of management,

including medication, and life events of children with dystonia. Opening this process to a wider clinical group could help to both highlight the plight and refine the management of dystonia this difficult clinical group.

Conclusion

Acute worsening dystonia is a clinical emergency, requiring prompt and proper management. The use of the dystonia severity action plan (DSAP) can help to recognise early signs of worsening dystonia and lead to intervention before status dystonicus is established.

Management of acute worsening dystonia is extremely challenging, with the most commonly used short-term management strategies of using benzodiazepines and opiates associated with a significant risk of severe respiratory depression.

High dose clonidine can be administered via IV or transdermal routes when ileus / gut-failure precludes the enteral route for the acute management of severe exacerbations of dystonia. Clonidine use in our small case-series was not associated with significant cardio-respiratory depression even at doses as high as 9 mcg/kg/hr but combination medication should be used with caution.

The need for 'emergency rescue medication for dystonia' in any 24 hour period should prompt an upward adjustment of the total daily dose of clonidine in divided doses if possible or continuous administration by the most convenient route.

Every route of administration has a drawback: waking the sleeping child to administer oral clonidine, the need to transfer to PICU or HDU for iv clonidine; the problems of administering clonidine when dealing with an ileus without intravenous access or infected iv lines that must be removed at night or at week-ends may be solved with transdermal clonidine.

In our hospital transdermal patches were less expensive than the equivalent intravenous preparation, but the health economics of transdermal administration, by preventing healthcare cost escalation, may be a viable alternative for medium to long-term use as in case 1 who has been on transdermal clonidine for 4.0 years.

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VN contributed to managing the children, wrote the initial draft and presented the work in part at the British Paediatric Association Annual Meeting 2016 in Sheffield, UK.

JPLin managed the children, conceived, designed, executed and co-wrote the initial draft and critically reviewed the manuscript. JPLin has received a Guy's and St Thomas' Charity New Services and innovation grant G060708; and Action Medical Research Grant AMR – GN2097 and grants from the Dystonia Society UK Grants 01/2011 and 07/2013 and unrestricted educational grants from Medtronic Ltd.

KW and AH contributed to data collection.

TA was in receipt of a NIHR Academic Clinical Lectureship and managed the children, contributed to data analysis, graph design, and critically reviewed the manuscript.

DL and MK managed the children and critically reviewed the manuscript.

ST supported the use of clonidine patches in the time-critical context of acute neurological deterioration, encouraged the preparation of this report and critically reviewed the manuscript.

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Figure 1. Case1: a. Nine-year old ex-25 week preterm twin boy in withdrawal status dystonicus (DSAP level 5 within 10 days after bilateral globus pallidus internus deep brain stimulation removal for battery-site erosion-infection. Enteral clonidine is replaced on day 6 by i.v. clonidine owing to a gut ileus. b. It takes 250 days for this child to consistently achieve comfortable sitting i.e. level 1 DSAP. Iv clonidine was eventually replaced by three 300microgramme/day transdermal clonidine patches on day 48, each of which have continued to the present time and the patches are changed every 7 days in rotation. For further details see text.

Figure 2. Case 2 : An eleven year old girl with PANK2 disease and severe generalized dystonia, GMCS level V, feeding via gastrostomy, was transferred from another tertiary referral centre due to acute worsening dystonia. On admission, sleep and sitting out in a chair were severely disrupted (DSAP grade 3). Gradual escalation of clonidine up to 2.1mcg/kg/hr over 18 days was administered enterally for dystonia control. Sleep improved by day 20 (DSAP Grade 2) and intermittent sitting out in her chair from day 16 (DSAP Grade 1). Deep Brain Stimulation was implanted as planned 3 months later.

Figure 3. Case 3: A seven year old girl with microcephaly, severe choreoathetoid movement disorder and profound developmental delay with no underlying diagnosis and GMFCS level V was admitted after Deep Brain stimulation surgery with severe hyperkinetic movements, worsening during an intercurrent respiratory infection. Escalation of oral clonidine up to 3.9mcg/kg/hour on day 15 resulted in a DSAP improvement from Grade 3 (unable to sleep) to DSAP Grade 1 on day 17 and also allowed weaning of nitrazepam and reduced the involuntary movements during the episode of infection.

Figure 4. Case 4: A fourteen year-old girl with early epileptic encephalopathy and choreoathetoid movement disorder, associated with GNAO1 mutation, GMFCS level IV presented to her local hospital with a severe dystonic-choreoathetoid crisis requiring admission to her Regional Paediatric Intensive Care Unit (PICU) for 5 weeks from which she was transferred to our unit for deep brain stimulation (DBS). Prior to transfer, management of the dystonic-choreoathetoid crisis was greatly helped by initiating a high-dose clonidine IV infusion at 3.5micrograms/kg/hour. This was subsequently converted to enteral clonidine via nasogastric tube infusion. This clonidine infusion allowed comfortable lying in bed and sleeping at night but sitting out in her chair only resumed after bilateral globus pallidus internus (GPi) DBS followed by gradual mobilisation leading to gradual clonidine weaning to zero prior to transfer back to her local hospital.

Figure 5. Case 5: A fourteen year old boy with dystonic-dyskinetic cerebral palsy and epilepsy, GMFCS Level V, severe sleep problems and jejunostomy feeding, presented in status dystonicus in July 2015, associated with septicaemia and ileus, after having bilateral hip surgery, requiring admission to PICU. He was started on IV clonidine, which helped his symptoms to settle gradually. There was a noticeable exacerbation of his dystonia during his treatment course, with increasing of DSAP score from 1 to 3, when the dose of clonidine was inadvertently reduced from 1mcg/kg/hour to 0.1mcg/kg/hour, followed by a quick response and clinical improvement once he was given the correct dose (figure 5).

Table 1- Dystonia severity assessment plan- DSAP criteria *DIC= disseminated intravascular coagulation	
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 medications.
3	Not able to tolerate lying and /or unable to get to sleep or sleep disrupted. No evidence of metabolic decompensation, CK<1000IU/L
4	Early multi-organ failure. Clinically as above with: Pyrexia (in absence of infection) Evidence of metabolic compromise (e.g. elevated potassium, low calcium, evidence of rising creatinine and /or urea) Evidence of myoglobinuria. CK>1000IU/L
5	Immediately life threatening Clinically as above with: Full metabolic decompensation Respiratory, cardiovascular, haematological (e.g. DIC*) or renal compromise requiring organ support Requires intensive care

Figure 1. Case1. Nine-year old ex-25 week preterm twin boy in withdrawal status dystonicus, DSAP level 5, within 10 days after bilateral globus pallidus internus deep brain stimulation removal for battery-site erosion-infection.

Top: The Dystonia Severity Assessment Plan (DSAP). It takes 250 days for this child to consistently achieve comfortable sitting i.e. level 1 DSAP.

Bottom: Bilateral Globus Pallidus Internus Deep Brain Stimulation (DBS, grey rectangle) is re-introduced on day 17 after a course of i.v. antibiotics. Enteral clonidine is replaced on day 6 by i.v. clonidine owing to a gut ileus (lower figure) and enteral clonidine re-introduced on day 25. I.v. clonidine was eventually replaced by three 300microgramme/day transdermal clonidine patches on day 48, each of which have continued to the present time and the patches are changed every 7 days in rotation. For further details see text.

Figure 2.

Case 2 . An eleven year old girl with PANK2 disease and severe generalized dystonia, GMCS level V, feeding via gastrostomy, was transferred from another tertiary referral centre due to acute worsening dystonia. On admission, sleep and sitting out in a chair were severely disrupted (DSAP grade 3). Gradual escalation of clonidine up to 2.1mcg/kg/hr over 18 days was administered enterally for dystonia control. Sleep improved by day 20 (DSAP Grade 2) and intermittent sitting out in her chair from day 16 (DSAP Grade 1). Deep Brain Stimulation was implanted as planned 3 months later.

Figure 3. Case 3. A seven year old girl with microcephaly, severe choreoathetoid movement disorder and profound developmental delay with no underlying diagnosis and GMFCS level V was admitted after Deep Brain stimulation surgery with severe hyperkinetic movements, worsening during an intercurrent respiratory infection. Escalation of oral clonidine up to 3.9mcg/kg/hour on day 15 resulted in a DSAP improvement from Grade 3 (unable to sleep) to DSAP Grade 1 (sitting comfortably) on day 17 and also allowed weaning of nitrazepam and reduced the involuntary movements during the episode of infection.

Figure 4. Case 4. A fourteen year-old girl with early epileptic encephalopathy and choreoathetoid movement disorder, associated with GNAO1 mutation, GMFCS level IV presented to her local hospital with a severe dystonic-choreoathetoid crisis requiring admission to her Regional Paediatric Intensive Care Unit (PICU) for 5 weeks from which she was transferred to our unit for deep brain stimulation (DBS). Prior to transfer, management of the dystonic-choreoathetoid crisis was greatly helped by initiating a high-dose clonidine IV infusion at 3.5micrograms/kg/hour. This was subsequently converted to enteral clonidine via a nasogastric tube infusion. This clonidine infusion allowed comfortable lying in bed and sleeping at night (DSAP grade 2) but sitting out in her chair (DSAP grade 1) only resumed after bilateral globus pallidus internus (GPi) DBS followed by gradual mobilisation leading to gradual clonidine weaning to zero prior to transfer back to her local hospital.

Figure 5. Case 5. A fourteen year old boy with dystonic-dyskinetic cerebral palsy and epilepsy, GMFCS Level V, severe sleep problems and jejunostomy feeding, presented in sub-status dystonicus, unable to sleep or sit (DSAP grade 3) in July 2015, associated with septicaemia and ileus, after having bilateral hip surgery, requiring admission to PICU. He was started on IV clonidine, which helped his symptoms to settle gradually. There was a noticeable exacerbation of his dystonia during his treatment course, with increasing of DSAP score from 1 to 3, when the dose of clonidine was inadvertently reduced from 1mcg/kg/hour to 0.1mcg/kg/hour, followed by a quick improvement in the DSAP score from level 3 to level 1 and clinical improvement once the correct i.v. clonidine infusion dose was administered.

Status dystonicus remains a complex multisystem disorder and usually involves a multidisciplinary approach.

Clonidine may provide a suitable alternative to benzodiazepines and opiate infusions in the management of childhood status dystonicus.

Clonidine doses of 0.5-3mcg/kg/hour (range 0.1- 9mcg/kg/hour) may be necessary to safely manage acute severe dystonia and in our experience does not result in severe hypotension or respiratory depression

Severe dystonia is effectively managed using the Dystonia Severity Assessment Plan (DSAP) scoring system which monitors worsening and improvement in dystonia based on meaningful function and comfort

Clonidine helps to restore sleep in dystonic children which in turn is crucial for breaking the vicious cycle of continuous muscular contraction of dystonia

Attention to the sleep patterns of children with dystonia and improving their often fragmented sleep forms the cornerstone of dystonia management