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Desmopressin as a therapy for nocturnal enuresis in patients with Sickle Cell Disease

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Background:

Nocturnal enuresis is more prevalent in patients with sickle cell disease (SCD) than the general pediatric population. The International Children's Continence Society (ICCS) defines enuresis as discrete episodes of urinary incontinence during sleep in children ≥5 years of age.[1] The rate of nocturnal enuresis in patients with sickle cell disease (Hemoglobin SS, SB^{0thal} and SB^{+thal}) ranges from 28%[2] to 52%[3] of boys and 11%[2] -38%[3] of girls, compared to 7% of boys and 3% of girls at age 5 in the general population.[2] Enuresis becomes less common with age, in one study decreasing from 36% in patients between 8-10 years to 9% of patients aged 18-20 years[4]. Nocturnal enuresis has been shown to affect patient's quality of life[5], and can lead to social and emotional stigma, stress and inconvenience. Currently, there is no mainstay of therapy for nocturnal enuresis in patients with SCD. In the general pediatric population, several therapies are used to manage nocturnal enuresis, including behavior modification, alarms and pharmacotherapy such as desmopressin and less often, imipramine. Desmopressin is a synthetic analogue of arginine vasopressin which exerts an antidiuretic effect by increasing water reabsorption in the distal tubules and collecting ducts of the kidneys. In the general pediatric population, bed-wetting was reduced by 1.34 nights per week (95% CI 1.11-1.57) in patients who received desmopressin compared to those who received placebo. Patients receiving desmopressin were almost twice as likely to achieve at least 14 consecutive dry nights compared to placebo[6].

Desmopressin is not systematically prescribed to patients with SCD who have nocturnal enuresis. This may be due to the thought that these patients have an irreversible and progressive defect in the renal medulla secondary to chronic sickling episodes, and desmopressin may be ineffective, as this defect is not related to the signaling pathways in which desmopressin acts. This also may be due to lack of adequately powered clinical trials demonstrating efficacy. More likely, patients with SCD have many medical complications associated with their disease and symptoms of seemingly lesser conditions such as nocturnal enuresis may be minimized or ignored.

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[1] Nevéus, T., et al., *The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardization Committee of the International Children's Continence Society.* The Journal of Urology, 2006. **176**(1): 314-324.

[2] Barakat, LP., et al., *Nocturnal Enuresis in Pediatric Sickle Cell Disease*. Journal of Developmental and Behavioral Pediatrics, 2001. **22**(5): p. 300-305

[3] Readett, D R J., et al., *Nocturnal enuresis in sickle cell haemoglobinopathies*. Archives of Disease in Childhood, 1990. **65**: 290-293

[4] DeBaun, M R., et al., *Enuresis Is a Common and Persistent Problem Among Children and Young Adults with Sickle Cell Anemia*. Urology, 2008. **72**(1):81-84

[5] Naitoh, Y., et al., *Health Related Quality of Life for Monosymptomatic Enuretic Patients and Their Mothers*. The Journal of Urology, 2012. **188**(5): 1910-1914

[6] Glazener CMA, Evans JHC. *Desmopressin for nocturnal enuresis in children.* Cochrane Database of Systematic Reviews, 2002, Issue 3. Art. No.: CD002112. DOI: 10.1002/14651858.CD002112

The mechanism underlying the higher prevalence of enuresis in patients with sickle cell disease is not completely understood. Several hypotheses have been studied and the etiology is thought to be multifactorial. The predominant theory proposes that enuresis occurs secondary to a defect in the concentrating capability of the kidney caused by the sickling of red blood cells in the hypertonic, acidic and hypoxic renal medulla. Sickling leads to occlusion of the vasa recta and impairment of blood flow.[7] This interferes with the countercurrent mechanism of the kidney, and impedes free water reabsorption leading to increased urinary volume, hyposthenuria and oftentimes delayed attainment of nocturnal urinary continence.

Several studies support this theory by demonstrating decreased urine osmolality in patients with sickle cell disease compared to healthy controls. Statius Van Eps et al, demonstrated that patients with Hemoglobin SS disease have decreased urine osmolality at a young age compared to patients with Hemoglobin SC, AS and AA, with a progressive decline over time until a plateau at approximately age ten.[8] Noll et al compared patients with sickle cell disease to sibling controls to demonstrate higher rates of enuresis and nocturia in patients with SCD correlating with decreased urine specific gravity measurements.[9] Readett et al challenged this hypothesis by comparing urine osmolality of enuretic patients with SCD to non-enuretic patients with SCD, demonstrating no significant difference in the urine osmolality after a water deprivation test between the two groups. Their study showed that enuretic patients had a lower maximum functional bladder capacity and higher overnight urine volume to bladder capacity ratio compared to controls, suggesting that these factors may contribute to enuresis in patients with sickle cell disease.[10] The study also collected subjective data from families who assessed patients with nocturnal enuresis as deep sleepers. In another study, Readett et al noted a correlation between large family size and likelihood of enuresis in boys[3], further suggesting a social and environmental component to enuresis.

Few studies have been done to evaluate the efficacy of standard therapies for nocturnal enuresis in patients with SCD. One study by Figueroa et al[11] supports the use of desmopressin in patients with SCD. This study examined a population of 91 patients with sickle cell disease age 6-21 with a 29.6% prevalence of nocturnal enuresis. The researchers looked at the effect of enuresis alarms and intranasal desmopressin on the rate of nocturnal enuresis. Ten patients elected to receive desmopressin, with four showing complete resolution of symptoms, and two showing greater than 50% improvement of symptoms while receiving medication, an overall 60% rate of improvement. Two patients elected to use enuresis alarms with no improvement in symptoms after three and four months respectively. While this study showed the desmopressin may be effective in this population, it was limited by its small sample size and lack of randomization or blinding. This study also used intranasal desmopressin, which is not routinely

[7] Becker, A, *Sickle cell nephropathy : challenging the conventional wisdom*, Pediatric Nephrology, 2011. **26**: 2099-2109

[8] Statius Van Eps, LW., et al,. *The relation between age and renal concentrating capacity in sickle cell disease and hemoglobin C disease*. Clinica Chimia Acta, 1970. **27**: 501-511

[9] Noll, JB,. et al., *Enuresis and Nocturia in Sickle Cell Disease*. The Journal of Pediatrics, 1967. **70**: 965-967

[10] Readett, D R J., et al., *Determinants of Nocturnal Enuresis in Homozygous Sickle Cell Disease*. Archives of Disease in Childhood, 1990. **65**:615-618

[11] Figueroa, E,. et al., *Enuresis in Sickle cell Disease*. The Journal of Urology, 1995. **153**: 1987-1989

used as it is associated with variable absorption patterns and thus increased side effects compared to the oral preparation, including the serious side effect of hyponatremia[6].

A survey conducted from July to September 2010 at the CHAM Hematology clinic, where we follow over 600 sickle cell patients, showed that of 63 patients between the ages of 5-21, 27% reported nocturnal enuresis. Table 1 shows rates of nocturnal enuresis by age group in this population. This data is consistent with the increased rate of nocturnal enuresis previously reported, suggesting that we will have a more than an adequate number of patients eligible to participate in this study.

Table 1

Age	**Enuretic**	**Non Enuretic**	**% Enuretic**
5-10	8	28	22.2%
11-21	9	18	33.3%
Total	17	46	27 %

Our initial objective was to conduct a randomized placebo controlled double blinded study to assess the efficacy of desmopressin on the rate of nocturnal enuresis in patients with SCD compared to placebo. We also planned to utilize quality of life and fatigue scale questionnaires to evaluate the quality of life in these patients prior to and after treatment. We hypothesized that patients receiving desmopressin would demonstrate fewer episodes of nocturnal enuresis compared to those receiving placebo. Due to low accrual with the study (five participants completed the study and nine participants withdrew from the study), and due to the fact that DDAVP treatment for nocturnal enuresis is already standard of care in a general pediatric population, it was determined beneficial by the investigators to prescribe DDAVP as standard of care and to eliminate the placebo group. The study team will prospectively collect quality of life data for the patients prior to prescribing DDAVP and then one month after initiating treatment with DDAVP. Prior to starting DDAVP an eligibility diary would be filled out on recollection by patient on their enuresis patterns for the past 2 weeks (Appendix 1A). Enuresis diaries would be given to patients and families to track their enuresis but also could be filled out retrospectively with study coordinator either in person or over the phone. We propose to then analyze their laboratory, physical exam, imaging, data prospectively for those patients administered DDAVP as part of their clinical care upon starting the DDAVP. We would prospectively administer surveys on willing participants prior to starting DDAVP and then one month into the intervention. To provide information to the sickle cell research community we propose the following interventions.

The primary objective of this study is:

1. To prospectively assess if the use of desmopressin in patients with sickle cell disease and nocturnal enuresis will decrease the number of nighttime episodes of enuresis by 50% after initiating DDAVP at 0.4 mg nightly dose with dose escalation as clinically appropriate.

Secondary objectives are:

1. To determine if patients with sickle cell disease and nocturnal enuresis receiving desmopressin will have an improved quality of life compared to their baseline.
2. To determine if patients with sickle cell disease and nocturnal enuresis receiving desmopressin will have less daytime fatigue compared to their baseline data.
3. To determine if the use of desmopressin in patients with nocturnal enuresis improves rates of nocturia, defined as episodes of nighttime awakening to void in children ≥5 years of age[12], compared to prior to initiating treatment with DDAVP.

Study Site:

This study will be implemented at the Children's Hospital at Montefiore (CHAM). Patients with sickle cell disease will be recruited from the Hematology outpatient clinic and inpatient unit.

Population:

Inclusion Criteria:

1. Patients with Hemoglobin SS, SC, SB^{0thal} or SB^{+thal}
2. Patients age 8-21
3. Patients with at least two episodes of primary nocturnal enuresis per week or four episodes over the two weeks prior to enrollment.
4. Patients with secondary enuresis who have been evaluated and cleared by a pediatric urologist as not having other etiologies of enuresis (e.g. overactive detrusor activity, a genitourinary anatomic abnormality)

Exclusion Criteria:

1. Patients with developmental delay or neurologic dysfunction secondary to stroke
2. Patients with hypertension or underlying renal disease.
3. Patients with genitourinary anatomic abnormalities. Any prior renal ultrasound showing normal genitourinary anatomy is sufficient to clear a patient for the study.
4. Patients with daytime urinary incontinence
5. Patients with glucosuria on urinalysis.
6. Patients with secondary nocturnal enuresis who have not been evaluated by a pediatric urologist to rule out other etiologies of enuresis.
7. Patients who are pregnant.
8. Patients receiving another medicine for nocturnal enuresis (e.g. imipramine).
9. Patients aged 8-17 who are experiencing pain.

[12] Nevéus T et al, The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol. 2006;176(1):314. Of note, the term nocturia does not apply to children who awaken for reasons other than a need to void.

Methods:

Subjects:
Patients will be recruited for the study in the CHAM outpatient hematology clinic and the inpatient Hematology unit. Medical staff will be educated about the study and designated individuals will obtain consent for administering the PROMIS Fatigue survey prior to initiating medication.

Enrollment:
This study will be a cohort analysis of a standard of care medication administered for nocturnal enuresis. Prior to starting this standard of care medication patients will fill out the PROMIS questionnaire on fatigue. Patients with sickle cell disease who fit the inclusion criteria will be notified about the study when they are seen in hematology clinic, prior to discharge from hospitalization or via phone by study staff. Patients enrolled during hospitalization will not start the trial until a post-hospitalization follow up visit. At this point, the study will be introduced and discussed. Written consent for the survey will be obtained from interested and eligible guardians, or patients, if they are older than 18 years old or an emancipated minor. Patients 7-17 years of age will sign assent. Patients will also be identified for eligibility via the electronic medical record. Patients who fit the inclusion criteria will be called and informed of the medication following a detailed script (see Appendix 6). If they are interested, consent will be obtained at the next outpatient or inpatient visit. Patients and/or guardians will have the option to decline participation or opt out of the study at any point.

Intervention
Patients if they meet eligibility criteria will be prescribed DDAVP starting at 0.4 mg every night. Baseline data will be obtained from all patients enrolled in the study using data from 6 months prior to initiating DDAVP. This includes medical history specific to SCD, general medical history (see Appendix 2A), baseline data and labs within the last 6 months (Appendix 2B-D). Renal sonogram will be obtained to assess baseline degree of fibrosis, unless patient has previous normal renal sonogram as part of standard of care.

The day that DDAVP is initiated, patients will complete the Promis Fatigue Scale to measure fatigue as a quality of life measure. We will repeat this questionnaire in a month after starting DDAVP.

Patients will receive 0.4 mg oral desmopressin tablet to be taken at bedtime and will receive similar instructions to take tablet at bedtime with minimal water. They will also be advised not to drink caffeinated beverages four hours before bedtime, not to drink any liquids after taking tablet, and to void right before bedtime. Patients will also be advised to discontinue medication if they develop symptoms of headache, nausea or vomiting, develop an acute illness, or if they are admitted to the hospital and are receiving intravenous fluids.

Monitoring
Patients will be asked to keep an "enuresis diary" for four weeks (See Appendix 1B). In the diary, patients will record their adherence to the medication, if they had an episode of enuresis, as well as the number of nighttime awakenings specifically secondary to nocturia (and not for

any other reason such as pain or anxiety). All patients will have a follow up call two weeks and four weeks after starting the medication by the study coordinator. Patients will be assessed for improvement in symptoms, medication adherence, and any side effects they are experiencing. Blood pressure, Chem-10, Urine and serum electrolytes and osmolality and urine analysis will be obtained if patient describes any adverse clinical symptoms as would be performed as part of standard of care. Enuresis diaries will be reviewed, and if patients do not have at least a 50% improvement in symptoms they will be advised to make an appointment to investigate if adjustment of the medication based on clinical care would be appropriate. See Appendix 3 for a complete study timeline.

Any patient that has a dose dependent side effect to the medication will have the dose reduced promptly and appropriate clinical management and follow up. If a patient has an acute VOC while taking study medication and is on intravenous fluids, the medicine will be held during the acute event. Individuals will be asked at the end of the study if they had a pain crisis or acute chest syndrome during this intervention.

Be advised that the patients will have up to one year to complete the study. Although the study should only take 4 weeks the patient will not be removed from study unless their participation lasts longer than one year. Children with sickle cell disease frequently have admissions related to their chronic disease that may prevent them from completing study within the 4 week time period. The medication works immediately and a stop in the medication will not cause a decrease in effect of the previous or current doses.

Study tools:

Promis Fatigue scale- PROMIS® instruments use modern measurement theory to assess patient–reported health status for physical, mental, and social well–being to reliably and validly measure patient–reported outcomes (PROs) for clinical research and practice [13,14]. PROMIS instruments measure concepts such as pain, fatigue, physical function, depression, anxiety and social function. The Fatigue scale utilizes a 7–day recall period (items include the phrase "the past 7 days") with five responses. The responses span from never (0) to almost always (4). The Fatigue scale is a 10 item questionnaire whose scores can be approximated if a participant skips a question. A 10-item short form can be scored as long as the participant answered at least 5 items. The Pediatric PROMIS Fatigue scale has been validated for patients aged 8-17 years of age. The surveys will be administered at initiation of medication (week 1) and after completion of 4 weeks of medication. If patients stop and restart the medication the survey will be taken after 4 consecutive weeks of at least 50 % compliance with the medication. This will assess differences in the patients' perception of fatigue after starting the medication. Please see Appendix 4 for Promis Fatigue Scale.

Statistics:

For our study, success in treatment will be defined as a 50% reduction in bedwetting episodes. Our primary endpoint is the improvement in number of wet nights (binary outcome variable) comparing pretreatment and post treatment use of desmopressin. We can expect little or no change in untreated subjects and therefore presume that maximum 10% will improve on their own. Based on the study by Figueroa et al,11 we can presume that 60% of patients will improve

with desmopressin treatment. In order to detect this 50% difference, we will enroll 50 patients for the study so that the 95% CI for proportion of subjects with improvement after treatment is expected to be (0.46, 0.74) thus will be able to exclude 10% that is expected for untreated subjects. In a secondary analysis, the improvement status will also be correlated to patient characteristics using a logistic regression model. Secondary endpoints are not powered

[13] Magasi, S. et al. (2011). Content validity of patient reported outcomes: Perspectives from a PROMIS meeting. Quality of Life Research, 25 Aug 2011.
[14]Garcia, S. F. et al. (2007). Standardizing patient–reported outcomes assessment in cancer clinical trials: a PROMIS initiative. Journal of Clinical Oncology, 25(32), 5106–12.

Risks/Assessment of Safety and Mitigation of Risks

The overall incidence of adverse events with the use of desmopressin in patients with nocturnal enuresis is low. Reported adverse events are described as mild and transient, including headache, abdominal pain, nausea and dyspepsia. Adverse events report in patients treated with the intranasal formulations also included nasal congestion, rhinitis and epistaxis. The most serious, but uncommon adverse event is hyponatremia, which can induce seizures. This is reported more commonly with the intranasal formulation, but has also been noted with the tablet form.[13] Robson et al looked at published data via Medline from December 1972 to August 2006 and post-marketing safety data from December 1972-June 2005 to assess the safety of desmopressin with a focus on the safety of the oral formulation. They identified 21 clinical trials on desmopressin use in children with nocturnal enuresis, in which there were no reports of hyponatremia. 21 publications were identified that included 48 case reports of hyponatremia, all of which were associated with intranasal desmopressin use. Post-marketing safety data reports identified 151 cases of hyponatremia in patients with nocturnal enuresis, 145 of whom were treated with the intranasal formulation and 6 of whom received the desmopressin tablet. Based on their review, Robson et al identified several preventable risk factors for hyponatremia, including avoiding high fluid intake, prescribing higher than recommended dose of medication, use of medication in patients younger than six years, and concomitant administration of another medication for nocturnal enuresis. They also recommend immediate discontinuing use of medication if patient develops symptoms of headache, nausea or vomiting, or if they develop an acute intercurrent illness, or are hospitalized and receiving IV fluids. Desmopressin package insert from Ferring Pharmaceuticals also recommends fluid restriction and recommend use with caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia[14].

In order to minimize the risk of an adverse event, patients will be given clear directions not to drink fluids after taking tablet. Patients will be advised to discontinue medication if they

[15]Robson, W.L.M., et al., *The Comparative Safety of Oral Versus Intranasal Desmopressin for the Treatment of Patients with Nocturnal Enuresis.* The Journal of Urology, 2007. **178** (1): 24-30
[16] Desmopressin Acetate Package Insert
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm215090.pdf

develop symptoms of headache, nausea or vomiting and contact their doctor immediately. Doses used in the study are within the recommended range of 0.2-0.6 mg. Patients receiving another medicine for nocturnal enuresis (e.g. imipramine) will not be included in the study. Side effects of the medication will be monitored at each follow up visit.

Refusal to participate in the study including answering surveys will have no effect on the care that the child or the parent/caregiver receives. If the patient wants to be prescribed DDAVP and not complete the rest of the study (diaries, surveys), since this is standard of care medication it will still be prescribed and monitored as clinically indicated.

Potential Benefits:

There is the potential to benefit directly from improvement of their enuresis and with that potentially improved quality of sleep and hydration status, both of which may are key factors in mitigating vaso-occlusive crises.

Data Safety Monitoring Plan

Data Quality

Data quality will be monitored by the investigators and DSMC. The following elements will be monitored: recruitment proceeding as expected; study subjects match the inclusion/exclusion criteria; deviations from the protocol; adverse events; accuracy and confidentiality of all information both in the case report forms and electronic databases. DSMC will meet after the first 20 patients are enrolled to assess the quality of the data.

Safety Monitoring

Safety monitoring will be conducted by the investigators and DMSC. All adverse events will be indicated on the source documentation for the study, and on the specific adverse event case report form. The following information about adverse events will be collected: 1) the onset and duration; 2) severity or intensity; 3) relationship to study drug; 4) action taken 5) outcome. The investigators will determine the severity of the event, assign attribution to event, and monitor the event until its resolution. For the purpose of this trial, the following conditions are expected due to the subject's underlying disease process or treatment and are not regarded as serious adverse events.

Expected AE due to sickle cell disease	**Expected AE due to sickle cell disease**	**Expected AEs due to IVIG**	**Expected AE due to narcotic usage**

Acute chest syndrome	Hyperplastic bone marrow	Asthenia	Constipation
Anemia	Hypoxemia (pO2 < 65 mm Hg)	Back pain	Hives
Aplastic crisis/anemia	Infection, encapsulated organism	Fever/Chills	Pruritus
Arthralgia	Jaundice	Cough	Respiratory depression
Avascular Necrosis of hip/shoulder	Leukocytosis	Headache	Urinary retention
Bone infarction	Meningitis	Hypertension	Nausea/vomiting
Cardiomegaly	Nausea and vomiting	Pharyngitis	
Cholecystitis	Pain, joints or long bones	Rash	
Cranial nerve palsy	Pain abdominal, chest, or back	Urticaria	
Decreased lung function	Priapism	Pruritis	
Delayed growth/puberty	Pulmonary hypertension	Dizziness	
Depressed ESR	Pulmonary infiltrates on CXR	Back pain	
Elevated serum bilirubin	Pyelonephritis	Arthralgia	
Elevated urinary urobilinogen	Renal papillary necrosis	Nausea/vomiting	
Fever	Reticulocytosis	Diarrhea	
Hand-foot syndrome	Retinal disease		
Hematuria	Retinal hemorrhage		

Hepatic sequestration	Rhabdomyolysis		
Hemolysis	Sepsis		
Hepatosplenomegaly	Skin ulcers		
Hyposthenuria	Splenic sequestration		

Adverse events (Grade 3-5 severity in the CTCAE of the latest version) will be actively tracked in real time on each patient.

Trial will be put on hold if any of the following criteria are met:

The trial will be put on hold (with no further subject enrollment and treatment) pending IRB and DSMC review if:

1) Cumulatively 2 patients experience an unexpected possibly related Grade 3 serious adverse event, or

2) 1 patient experiences an unexpected possibly related Grade 4-5 serious adverse event, or

3) 1 patient experiences an unexpected possibly related seizure episode of Grade 3 severity or higher.

The determination of whether the adverse event is definitely related to DDAVP or not will be made by the IRB, and DSMC and accordingly a decision to stop the trial completely or proceed will be made by both agencies. No study enrollment or treatment will occur while the triggering event is being reviewed.

Data Safety and Monitoring Board

Data quality will be monitored by an independent 3-person DSMC board appointed from within the institution to ensure safe and effective conduct of the trial and recommend conclusion of the trial if significant risks have developed or the trial is unlikely to be concluded successfully. The board members are i) a pediatric hematologist/oncologist knowledgeable in sickle cell disease not involved in the trial (Dr. Alexander Chou); ii) Dr. Michael Rinke, a pediatric hospitalist who is a quality expert and with knowledgeable in statistics and study design iii) Dr. Kimberly Reidy, a pediatric nephrologist and iv) Dr. Xiaonan Xue, a statistician in the department of epidemiology and population health. Dr. Alexander Chou will be the executive secretary of the

DSMC. The DSMC will meet with the Principal Investigator after the first 20 patients have completed the trial and then at the end of the trial and perform the following activities:

a. Assess participant safety, including:
    i. All protocol deviations and adverse events
    ii. All scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.
    iii. Benefit/risk ratio of procedures and participant burden
b. Evaluate trial progress, including:
    i. Quality, accuracy, and timeliness of collected data and statistical analysis
    ii. Selection, recruitment, and retention of participants
    iii. Confidentiality of trial data
    iv. Efficacy of the study intervention
c. Performance of clinical research sites, including:
    i. Performance of clinical research pharmacy and the core lab
    ii. Adherence to protocol requirements
d. Make recommendations to the IRB and investigators, including:
    i. Continuation or conclusion of the trial
    ii. Amendments to the study protocol and consent forms

Protection of Privacy:

Patient data will be confidential and only personnel directly involved in the study will have access to it. All patient data will be coded and entered into a password protected electronic database.