Assessing the feasibility of n-of-1 trials in children with hypertension and chronic kidney disease

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Assessing the feasibility of n-of-1 trials in children with hypertension and chronic kidney disease: a pilot study

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Background

Hypertension (HTN) and kidney disease are closely linked disease states, in that uncontrolled blood pressure (BP) contributes to acceleration of kidney disease, and as kidney function worsens, BP becomes more difficult to control.[1,2] Despite the widespread use of antihypertensive medication in children with chronic kidney disease (CKD) and end-stage renal disease (ESRD), BP often remains uncontrolled in this particularly vulnerable population.[3] Cardiovascular (CV) disease is a leading cause of morbidity and mortality among patients with ESRD,[4] yet robust evidence to guide therapeutic decisions is lacking. Pediatric HTN treatment studies have been limited primarily to small, industry-sponsored drug trials and large-scale comparative effectiveness trials are not anticipated given sample size limitations.[5] National pediatric guidelines recommend renin-angiotensin-aldosterone system (RAAS) inhibition as the preferred first-line therapy for hypertensive patients with CKD, but it is unknown whether individuals will exhibit heterogeneity of treatment effects to the various widely used and commonly available options within this drug class.[6] The drug that works best overall in a traditional parallel group trial may not be best for the individual patient, depending on a variety of factors that can affect treatment response, including etiology of renal disease, concurrent medication use, age, ethnicity, obesity status, and genomic factors. To address this problem, we will investigate whether n-of-1 trials to personalize treatment decisions result in improved clinical outcomes compared to usual practice.

N-of-1 trials are single patient randomized controlled trials (RCTs) that systematically compare various therapeutic options in the patient in a crossover fashion, applying techniques borrowed from traditional trials to minimize confounding and bias.[7] The results are used to inform treatment decisions for the individual patient and in some circumstances can also be aggregated across participants to produce population-level estimates.[8] Although n-of- trials were first proposed decades ago, their potential value is now being more widely recognized.[9-11] However it is unclear whether their potential benefits would justify the effort required to use them in clinical practice.[12] We propose a series of n-of-1 trials in hypertensive children with CKD and ESRD to determine if ambulatory BP control is improved after the antihypertensive regimen is modified based on the results of an n-of-1 trial.

With KL-2 funding we previously conducted a series of n-of-1 trials with repeated ambulatory BP monitoring (ABPM) in 42 children with primary HTN, and found them to be useful to differentiate drug response. In that study, n-of-1 trials were designed to identify which of three commonly used medications (amlodipine, hydrochlorothiazide (HCTZ), and lisinopril) when prescribed as monotherapy produced the greatest ambulatory BP reduction for the individual patient without unacceptable side effects. This study, HSC-MS-13-0287: “Individualizing the treatment of essential hypertension in adolescents using n-of-1 trials”, was determined to be a QI activity by the UTH IRB. We recruited patients from our pediatric hypertension clinic from June 2013 to July 2016. Among 55 patients meeting inclusion criteria, 42 (76%) agreed to participate in an n-of-1 trial with little urging. In this sample (N=42) no single drug emerged as the preferred therapy for the majority of patients, with amlodipine selected for 19%, lisinopril 38%, HCTZ 10%.[13] The n-of-1 trial resulted in drug discontinuation in 17% and BP remained uncontrolled on a single drug in 10%.

These results prompted our consideration of whether n-of-1 trials should be incorporated into routine clinical practice. To test whether n-of-1 trials produce improved clinical outcomes compared to usual care, we were awarded the UTHealth Learning Healthcare Scholars award to conduct a single center parallel group RCT comparing n-of-1 trials to usual care in our pediatric HTN clinics. We have randomized 49 participants since 2018 and enrollment is ongoing. For this study, HSC-MS-17-1014: “N-of-1 Trials in Children with Hypertension (NICHE): A Randomized Clinical Trial of the N-of-1 Trial Approach”, verbal informed consent is obtained with waiver of documentation of consent.

Our previous work has been limited to patients without significant comorbidities, whose BP is likely to be well-controlled with one or two antihypertensive drugs. We have not yet studied what role n-of-1 trials can play in the care of children with CKD, ESRD or after kidney transplantation, whose HTN management strategy differs greatly from children with primary HTN.

Specific Aims

HTN contributes to progression of renal failure and is an important modifiable risk factor for CV morbidity/mortality. Little is known about whether any specific medications are more effective than others in reducing BP for children with kidney disease, or whether group-level treatment recommendations would be appropriate at all. Limited work has been done to characterize national practice variation of pharmacologic management of HTN in pediatric CKD/ESRD.[14] Given the complex interaction of many factors in the pathophysiology of HTN in CKD, including sodium retention, volume expansion, RAAS activation, sympathetic nervous system over-activity, and endothelial dysfunction, n-of-1 trials may be the best strategy to systematically individualize the HTN management approach in this high risk, yet understudied population. In view of the high baseline risk for CV morbidity in children with kidney disease, it is especially important to determine whether n-of-1 trials should be used to optimize BP control for these individuals, which could slow the decline of kidney function and reduce CV morbidity and mortality.

The funding requested will allow our team to capitalize on our unique expertise in n-of-1 trials and advance the field by assessing their feasibility in children with CKD/ESRD at our center. We propose a series of customizable n-of-1 trials to individualize the antihypertensive drug regimen prescribed to pediatric patients in our outpatient nephrology clinics and dialysis unit. The experience and data from the proposed pilot study will be an indispensable preliminary step towards our next goal: to design and conduct a multi-center RCT among children with CKD/ESRD to test whether n-of-1 trial guided decision-making improves BP control compared to current usual practice. **Central hypothesis:** BP control will be improved for the individual patient after the antihypertensive drug regimen is modified based on the results of an n-of-1 trial. **Rationale:** In the absence of robust evidence, prescribing decisions are often informed by clinician preferences, anecdotal experience, and trial-and-error. Instead, n-of-1 trials can provide patient-derived data to inform management decisions and reduce the guesswork inherent in usual practice. Our prior work showed that n-of-1 trials were well accepted in children with primary HTN, and led to a change from pre-trial antihypertensive therapy in 75% of participants.[15] We are currently testing whether the antihypertensive drug regimen that is informed by an n-of-1 trial produces improved BP control compared to usual practice in an ongoing RCT among children with primary hypertension at our institution. The proposed project will allow us to assess whether n-of-1 trials are feasible in the management of HTN associated with kidney disease, and could directly lead to a future funding proposal for a larger multicenter RCT assessing generalizability to other centers and whether this approach results in improved patient outcomes. **Qualifications:** This pilot funding proposal builds on the productivity, infrastructure, and investment by our team in the design and implementation of n-of-1 trials.[15-19]

Aim 1: To assess the safety and feasibility of n-of-1 trials in children with CKD/ESRD. After offering an n-of-1 trial to all patients at our center who meet eligibility criteria, we will report the % of eligible patients who agree to participate, and % that start but do not complete the protocol as planned. We will explore reasons cited by patients or clinicians for declining to participate or deviation from n-of-1 protocol. Upon completion, perceived harms from participation, including HTN-related complications will be described.
Hypothesis: N-of-1 trials will be well-accepted in this population and will not be associated with significant adverse effects.

Aim 2: Investigate whether the use of n-of-1 trials to modify antihypertensive treatment strategy improves BP in children with kidney disease. 24-hour ABPM will be conducted at enrollment and at 6 months to compare BP (24-hr MAP) before and after the drug regimen is modified based on n-of-1 trial. We will also assess the % of participants who achieve target BP (24-hr MAP to <50th %ile) as recommended for this population.[6]
Hypothesis: When antihypertensive medications are prescribed based on the results of an n-of-1 trial, the resulting drug regimen will be more effective in BP reduction for the individual patient, compared to the pre-n-of-1 regimen.

Aim 3: Describe treatment strategies in the management of hypertension in children with chronic kidney disease at major pediatric centers nationally. The PEDSnet database will be queried to provide a description of treatment strategies including frequency of use of particular HTN drugs, number of drugs prescribed per patient, and longitudinal description of changes in BP m a over time.
Hypothesis: Prescribing practices vary greatly by center.

The overarching goal of this proposal, which addresses key knowledge gaps in the management of hypertension in pediatric kidney disease and in the design and conduct of n-of-1 trials, is to develop a deeper understanding of the feasibility and generalizability of n-of-1 trials to children with kidney disease. If we find that BP control is improved when the drug regimen is modified based on an n-of-1 trial, this approach should be tested more rigorously in a multicenter RCT. Our next step also may include the development of a decision support tool informed by the results of previous n-of-1 trials to provide Bayesian probabilities of treatment success with various treatment strategies based on patient characteristics. If shown to improve the management of HTN in patients with CKD/ESRD, this could result in improved long-term BP control and intermediate CV outcomes, and holds potential to slow the progression of renal disease in children.

Research Approach

We propose a series of n-of-1 trials in hypertensive children with CKD/ESRD to assess within patient variation in BP response, and to ultimately inform the treatment strategy for the individual patient.

Population/setting: We will recruit from the clinical practices affiliated with the UTH Division of Pediatric Nephrology & Hypertension, including outpatient nephrology clinic at UTPhysicians, the nephrology clinic at the Pediatric Transplant Center and the chronic dialysis unit at Children's Memorial Hermann Hospital (CMHH).

Eligibility: Inclusion criteria: children and adolescents 5-22 yrs old, with hypertension and CKD stage 2-5, and requiring antihypertensive medication per clinician judgement. BP control at enrollment (whether well-controlled or uncontrolled on current regimen) will not affect eligibility status. Exclusion criteria: renal transplant anticipated or occurred within 6 months of screening, transfer out of our practice setting anticipated within 6 months, unable to complete 24 hr ABPM due to developmental or behavioral limitations.

Screening: Electronic health record data will be pre-screened with a one-time structured data query by the UTH School of Biomedical Informatics to identify patients within 5-22 yo, with relevant ICD10-CM codes (HTN: I10-I16, CKD: N18*, dialysis-dependent: Z99.2, or kidney transplant status: Z94), and seen by a pediatric nephrologist within 12 months. These records will be reviewed to exclude those who do not meet eligibility criteria. The remaining patients will be considered eligible and will be entered into a REDCap database.

Recruitment: For clinic CKD patients, recruitment will take place during a routine nephrology clinic visit. Clinicians will be emailed once weekly with a list of all eligible patients scheduled to be seen that week. For dialysis-dependent ESRD patients, recruitment will take place during a routine dialysis visit in September 2020. A brief recruitment video (online) will be viewed by patient and caretaker from clinic room computer and followed by face to face discussion with nephrologist (all of whom are co-investigators). The video will introduce the concept of therapeutic uncertainty and will delineate the n-of-1 trial protocol and the procedures for the baseline and 6 month assessments.

Consent: Patient verbal assent and caretaker verbal consent will be obtained before enrollment. This consent procedure was previously approved by the UTH IRB committee for a similar protocol in children without CKD.

N-of-1 trial protocol:

The n-of-1 trial will be customized for the individual patient to test which treatment strategy produces superior BP reduction without unacceptable side effects. After discussion with the patient/caregiver to identify whether they have specific concerns about particular medications, the nephrologist will decide which two drugs and dosages will be tested in the n-of-1 trial. Drugs from the α-blocker and β-blocker drug classes will not be eligible for testing due to the risk of withdrawal syndrome associated with abrupt cessation. These and all other previously prescribed antihypertensive drugs not being tested will be continued at unchanged doses during the n-of-1 trial.

The two drugs will be assessed at clinician-selected dosing in a randomized treatment order (ex ABAB), for two weeks per treatment period and two treatment periods per drug with increasing doses assessed for additional treatment periods if BP remains elevated with initial dosing of both regimens. Treatment response for each regimen will be measured with a side effect survey administered to patient/caregiver and 24 hour ABPM (Spacelabs) on day 14 of each 2-week treatment period. ABPM readings every 20 min for

24 hours. For patients unwilling or unable to undergo repeated ABPM, home BP monitoring (Qardioarm) will be used, (mean of 3 readings, 1 minute apart) twice daily on days 13 and 14 of each 2-week treatment period.

Blinding can be employed in n-of-1 trials to minimize biased assessments of treatment effects. In our past studies, we have not made any attempt to mask patients/caregivers to the current treatment. In the present study, we will offer blinding to each patient/caregiver to assess the acceptability of blinding. If the family declines blinding, then the reasons will be recorded. If they agree to be blinded, patients will be advised to fill both prescriptions at the start of the trial. Medication will be dispensed by the patient's usual retail pharmacy with costs covered through usual insurance coverage. Caregivers who opt in to blinding will provide the research team with the dispensed medications, who will sort out the pills into a 31 day pill organizer according to the randomized treatment order and refill as needed once monthly. While a patient could theoretically decipher their treatment based on pill appearance, those who opt in to blinding are less likely to attempt to unblind themselves. Additionally, costly pharmacy fees would make other blinding approaches less feasible within the funding limitations of the current pilot award.

At the conclusion of all treatment periods, the clinician will review the BP and side effect survey findings with the family via either an in person or telemedicine visit. When the patient, caregiver, and clinician jointly conclude that there is a sufficiently high probability that the preferred treatment has been identified (defined as that which produces superior BP reduction without unacceptable side effects), it will be prescribed for long-term use along with all other previously prescribed antihypertensive medications, and the n-of-1 trial will conclude.

Aim 1: Assess the safety and feasibility of n-of-1 trials in children with CKD/ESRD.

Hypothesis: N-of-1 trials will be well-accepted and will not be associated with any significant adverse effects.

Acceptance rate will be tracked for all eligible patients who were offered enrollment. The nephrologist may decline without discussing first with the patient, and the patient/caretaker may decline after discussing participation with the nephrologist. Reasons for declining (by both clinician and patient/caregiver) will be collected in free text format in REDCap. Upon review of reasons for declining, emergent themes will be reported.

Completion rate will be tracked for all enrolled patients. Participants may withdraw at any time. At 6 months, all enrolled participants will be categorized according to their level of adherence to the n-of-1 trial protocol. Reasons for variance from the protocol will be recorded. We will explore whether any patient or clinical characteristics are associated with increased likelihood of deviation from the protocol.

Safety of participants will be carefully monitored. Clinicians will be encouraged to continue their usual practice of checking bloodwork within 1-2 weeks of starting certain medications (RAAS inhibitors, diuretics) to assess for clinically important changes in electrolytes or serum creatinine, which will be recorded along with adverse events or side effects which lead to early termination of a treatment period. At 6 months, the clinician will complete a safety form to report any additional harms which might have been linked to participation.

Data on acceptance, completion, and harms is critical in understanding the feasibility of this approach in this population, and will be of broad interest in the field of n-of-1 trials. This information will help us in future studies to adapt our approach and protocol to better meet patient and clinician preferences.

Aim 2: Investigate whether the use of n-of-1 trials to modify antihypertensive treatment strategy improves BP in children with kidney disease

Hypothesis: When antihypertensive medications are prescribed based on the results of an n-of-1 trial, the resulting treatment strategy will be more effective in BP reduction for the individual patient when compared to the BP with the pre-n-of-1 drug regimen.

Outcome measurement: 24-hr average of mean arterial pressure (MAP) on ABPM will be assessed before and after treatment strategy is informed by the n-of-1 trial.

- Baseline BP assessment: Shortly after enrollment, 24 hr ABPM will be performed to assess BP control on current (pre-n-of-1) antihypertensive treatment strategy.
- Final BP assessment: At 6 months after enrollment, regardless of when n-of-1 trial was completed, 24 hr ABPM will be performed to assess BP control on current treatment strategy (post- n-of-1).

1º outcome: Change in 24-hr MAP (from baseline to final)

2º outcome: Proportion of participants with target BP (24-hr MAP to <50th %ile)[6] (from baseline to final)

Sample size: We plan to enroll as many patients as feasible during the funding period. Based on our estimates of number of potentially eligible patients and our previous acceptance rate, we anticipate enrolling 20 patients.

Analytic approach: The primary outcome of 24-hr MAP will be analyzed by generalized linear mixed model (GLMM) accounting for repeated ABPMs over the study period including the pre-n-of-1 ABPM assessment. The mixed model will contain a random intercept for each patient and appropriate link function based on the distribution of the 24-hr mean MAP. From this model, we will report the average difference between 24-hr MAP at 6 months and baseline ABPM. Success for the n-of-1 trial will be defined as any decrease in mean 24-hr MAP at 6 months compared to pre-n-of-1 ABPM. Bayesian models with uninformative, neutral priors for regression coefficients and error variances will be used to determine the probability of decrease in 24-hr MAP after the n-of-1 trial. All analyses will be conducted on an intention-to-treat basis with the GLMM allowing inclusion of patients with missing BP measurements at some time points. Secondary binary outcome of 24-hr MAP to <50th %ile will be similarly analyzed over the study period to determine if the proportion of patients with 24-hr MAP to <50th %ile is greater after the n-of-1 trial. If the sample size allows, exploratory analysis will examine strata specific effects for sex, age group, race, BMI, CKD stage, medication class, and number of anti-hypertensive medications.

Aim 3: Describe treatment strategies in the management of hypertension in children with chronic kidney disease at major pediatric centers nationally (retrospective cohort study of de-identified multicenter dataset that does not include patients from our institution).

Our current and previous n-of-1 trial protocols were designed based on our local prescribing preferences in HTN management. As we prepare to design a future multicenter RCT, it will be essential to better understand national prescribing patterns to inform the design of n-of-1 trial protocols that are generalizable and broadly appealing to pediatric nephrologists at other centers. Previous large studies describing antihypertensive medication prescribing patterns in childhood kidney disease have been limited to cross-sectional design,[14] but the proposed observational study would allow longitudinal descriptions of treatment patterns within an individual over time.

Working with a data science team at CHOP, we will explore PEDSnet data to characterize BP phenotype in children with CKD/ESRD and describe common treatment strategies. Our search will be restricted to patients <18 years old who have been seen by a nephrologist, diagnosed with CKD or with an estimated GFR <90 ml/min per 1.73 m^2 on 2 occurrences separated by 90 days.

In addition to demographic factors (age, gender, race/ethnicity), we will describe other clinical factors (obesity, etiology and staging of CKD) and blood pressure phenotype, including modality of BP measurement, degree of elevation, frequency of repeated readings in a single visit, and number of visits until HTN is diagnosed.

We will describe what % of patients with CKD are diagnosed with HTN, and what % are prescribed antihypertensive medications. We will describe frequency of use of particular HTN drugs and drug classes, number of HTN drugs prescribed per patient, and longitudinal description of changes in management over time (ex. typical first/second line choices, and interval between dose and drug changes).

Analytic approach: To describe longitudinal hypertensive treatment patterns in children with CKD across multiple pediatric centers we will use generalized multilevel mixed models with appropriate link functions and two-level random effects for correlated observations within patient and within site. The analysis will be tailored to the available data once the PEDSnet variable set has been identified. The primary outcomes include

antihypertensive medication as binary (yes/no) or count (number of medications) stratified by medication class if available. Treatment patterns for these primary outcomes will be examined over time and across strata (BP level, severity of hypertension, CKD etiology, gender, age) as available.

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