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Clonidine for sedation in infants during therapeutic hypothermia with neonatal encephalopathy: pilot study

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Abstract

Objective: To determine a safe dose of clonidine (CLON) to be used in infants with hypoxic ischemic encephalopathy (HIE) undergoing therapeutic hypothermia (TH).

Study Design: A pilot prospective study was performed to determine the effect of CLON on autonomic parameters, the pharmacokinetics (PK) of CLON, and the amount of morphine (MOR) given “as needed” for shivering and agitation in a cohort of infants (n=12) with HIE undergoing TH compared to a historical control group (n=28).

Results: The CLON group received less “as needed” MOR than the MOR-only group for agitation/shivering ($p < 0.001$), and the CLON vs MOR-only group spent 92% vs 79% of cooling time at the target core body temperature (CBT; $p = 0.03$, CLON vs MOR).

Conclusions: Intravenous CLON (1mcg/kg Q8h) is well tolerated in infants treated with TH for HIE. CLON stabilizes CBT in the ideal range during cooling which may be optimal for neuroprotection.

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INTRODUCTION:

To date, therapeutic hypothermia (TH) is the only intervention known to be effective in reducing neonatal morbidity and mortality produced by hypoxic ischemic encephalopathy (HIE) (1). Even though neonates are reported to use nonshivering thermogenesis only in cold environments, infants undergoing TH with core body temperatures (CBT) between 33 and 34°C do shiver (2). In preclinical models, shivering and agitation inhibit the neuroprotective effects of TH (3). While routine administration of sedatives and analgesics to infants undergoing TH is not standard of care in all centers (4), some of these infants have significant agitation and shivering and do receive escalating doses of sedative-analgesics, which can cause respiratory depression. Thus, some centers report routine administration of sedative-analgesics as standard of care in infants undergoing TH (4), a practice that was also standard of care in our neonatal intensive care unit (NICU) at Johns Hopkins, the study site.

It is also unclear whether sedative-analgesics improve or worsen neurological outcomes in infants and children and whether different classes of sedative-analgesics confer more or less neuroprotection. Morphine is the most common sedative-analgesic used in infants and children during critical periods of brain development. While morphine exposure *in vitro* induces apoptosis of human microglia and neurons (5), no definitive consensus has been reached as to whether low-dose morphine exposure in critically ill newborns is associated with adverse long-term neurological outcomes. However, morphine exposure is associated with longer length of hospitalization, mechanical ventilation, and longer time to full feeds without clear evidence of neuroprotection. Therefore, determining the effects of other sedative-analgesics on short and long-term outcomes in newborns with brain injury is important (6).

Central α_2-adrenergic receptor agonists modify the central thermoregulatory set points for shivering and sweating, and thus are more effective in reducing postoperative shivering than opioid receptor agonists (7). Furthermore, α_2-adrenergic agonists provide mild analgesia, sedation without respiratory depression, and neuroprotection in newborn and adult models of brain injury (8–12). Clonidine is an α_2-adrenergic receptor agonist that is broadly used in infants and children with an overall good safety profile (13, 14). However, there is a lack of sufficient evidence regarding the choice of sedative-analgesic agent to control shivering and agitation and preserve respiratory drive among HIE babies undergoing TH. Moreover, how immaturity, end-organ damage, and TH affect the pharmacokinetics (PK) of specific α_2-adrenergic agonists has been recently published for dexmedetomidine (15), but not for clonidine.

Thus, we designed a pilot study with the primary objective to determine a safe dose of clonidine that could be used in infants with HIE treated with TH. Specifically, we determined (1) the effect of clonidine on autonomic parameters (blood pressure, heart rate, CBT, and time to rewarming), (2) the amount of opiate given for agitation and shivering while on clonidine, and (3) the PK of clonidine in 11 infants during TH. Fluctuations in CBT during TH, time to rewarm, and the amount of morphine given for agitation and sedation were compared between the infants who received clondine and an historical cohort who received scheduled morphine.

METHODS:

Design and Study Subjects:

A prospective interventional cohort study was conducted at Johns Hopkins Hospital (JHH) from March 2013 through April 2015. The study was reviewed and approved by the Institutional Review Board (IRB), conducted under Investigator New Drug (IND) approval from the FDA (123790) to use intravenous (IV) clonidine in infants with HIE for sedation during TH, and registered with clinicaltrials.gov (NCT01862250). The pilot trial was designed to determine the clonidine dose that would be well tolerated in HIE infants undergoing TH. For this pilot study, we decided *a priori* to enroll a convenience sample of 8 infants who received the same dose of clonidine that was well tolerated. Infants were eligible for inclusion if they had a gestational age ≥ 35 weeks, birth weight ≥ 1800 g, diagnosis of HIE requiring TH, parental written consent (English or Spanish), and attending neonatologist agreement to enroll the neonate. Infants were excluded if they were considered moribund; suspected of chromosomal anomaly and major cardiovascular anomaly; had hypotension that required ≥ 15 mcg/kg/min of dopamine or dobutamine or ≥ 2 vasopressors to maintain mean arterial pressure (MP) ≥ 45 mmHg; had a baseline heart rate < 80 bpm during therapeutic hypothermia; received inhaled nitric oxide (iNO) for hypoxemia; or ventilated with high frequency oscillating ventilation (HFOV). At the time of the study, HFOV was used in those infants with more significant respiratory failure.

For comparison, we obtained data from a retrospective cohort of 28 infants who were diagnosed with HIE, treated with TH, and born 6 months prior (September 2013–February 2014) or 6 months after (May 2015–November 2015) the clonidine trial. We selected these 6-month timeframes that straddled the interventional trial to control for the effect of practice change over time. All study infants were born at or transferred to JHH within 6 hours of birth for TH for the treatment of HIE. Written and informed consent was obtained for neonates enrolled in the clonidine trial. The IRB waived consent for the control group of neonates whose data were retrospectively examined.

Study Protocol:

As per standard of care in our NICU at the time, infants were routinely started on morphine (0.1 mg/kg) followed by (0.05 mg/kg/dose Q6h) at the start of TH. Once infants were enrolled in this study, routine dosing of morphine was discontinued, but infants could receive “PRN” morphine (0.05 mg/kg/dose) for agitation/shivering at the discretion of the clinical team. All doses of IV morphine were recorded. Vital signs were obtained at baseline and at Q10, 20, and 30 mins after the completion of the 30 min infusion of clonidine. Inotropes were titrated and fluid boluses were administered to maintain MAP ≥ 45 mmHg, which is the standard of clinical care in our NICU. At the time, dopamine was the first-line vasopressor in our NICU followed by dobutamine.

Clonidine dosing: Per study protocol, clonidine was administered when infants had a HR ≥ 90 bpm and MAP ≥ 45 mmHg, and infants required < 15 mcg/kg/min of dopamine or dobutamine to maintain this MAP. Clonidine was discontinued and no additional clonidine was administered if one of the following occurred:10 mmHg reduction in MAP from

preclonidine levels; MAP ≤ 40 mmHg requiring ≥ 20 mcg/kg/min of IV dopamine to recover the blood pressure within 15 mins of the drop in blood pressure associated with clonidine administration; HR ≤ 70/min at any time within 30 mins of the completion of the IV infusion of clonidine.

Blood was drawn to assay for clonidine plasma levels. The initial clonidine dose (1 mcg/kg Q6h) was chosen based on population PK data (with modifications) obtained from term infants of similar gestational age, weight, and postnatal age who were treated with clonidine (Duraclon™) orally for the treatment of neonatal abstinence syndrome (NAS) (14). Duraclon™ is formulated for epidural use. The same formulation was used in this study. Clonidine is mostly cleared by the kidneys and renal failure significantly delays its clearance.

We have previously shown that IV gentamicin (another drug primarily cleared by the kidney) clearance is reduced by 25% in a similar population of infants with HIE during TH (16). More recent studies published after our trial suggest that TH reduced clearance of aminoglycosides by 40% (17). Based on our published study (16), we reduced the dose of clonidine by 30% (1 mcg/kg Q4h) that was used in infants with NAS; thus the starting dose of clonidine in this HIE population was 1 mcg/kg Q6h.

The protocol was written such that this initial dose would be given to a minimum of 3 infants and that clonidine would be administered during both the cooling and rewarming phase of TH and weaned over 48 hours by 0.5 mcg/kg/day to prevent rebound hypertension that can occur post discontinuation of clonidine. The interval would be increased (Q8h or Q12h) for the subsequent group of infants based on the physiological responses, specifically cardiovascular instability requiring intervention (increased in inotropic support fluid and boluses as outlined above). After review of the first 4 cases, we decided that a minimum of 6 infants would be treated with the same tolerable dose and clonidine would only be administered during the cooling phase of TH and discontinued within 4 hours of the start of rewarming. A safety monitor (neonatologist) who was not part of the investigative team reviewed each case in detail for safety and made the decision to continue enrollment at the current interval or to modify the dosing interval. We stopped enrollment after a convenience sample of 8 infants who received the same dose of clonidine that was well tolerated and who had blood sampling for PK analysis of clonidine.

Therapeutic Hypothermia: All infants enrolled in the study were diagnosed with HIE based on the National Institute of Child Health and Human Development Neonatal Research Network's clinical trial of hypothermia in neonatal HIE (1, 18). Neonates received whole-body TH with a cooling blanket (Mul-T-Blanket Hyper/Hypothermia Blanket and Mul-T-Pad Temperature Therapy Pad; Gaymar Medi-Therm III; Gaymar Industries Inc., Orchard Park, NY) to maintain a rectal temperature of 33.5 ± 0.5°C for 72 hours. Per standard NICU protocol, neonates were rewarmed by increasing the temperature of the blanket by 0.5°C/hour until the infant had a CBT of 36°C. These infants (1) could receive sedation-analgesia "PRN" doses for agitation/shivering as determined by the clinical team, (2) were monitored for clinical and electrographic seizures, and when present were treated with phenobarbital only and with fosphenytoin, levetiracetam, or topiramate for persistent seizures, and (3)

were assessed for cerebral edema with head ultrasounds upon NICU admission, and for brain injury with MRI when the patient was hemodynamically stable after rewarming. Clinical variables, including vital signs and laboratory measurements, were extracted from a replicated database of the electronic medical record.

Clonidine Assay:

Clonidine samples were obtained at random time points. Whole blood (500 μL) was collected in a lavender BD Microtainer® containing K_2EDTA and refrigerated for < 24 hours. It was then centrifuged for 10 min and the plasma (~200 μL) was aspirated. Samples were stored at −80°C for 4–7 weeks prior to being assayed for clonidine. 50 μL of 0.1M sodium hydroxide was added to the plasma sample followed by liquid-liquid extraction with methyl t-butyl ether to extract clonidine. The supernatant was evaporated to dryness under nitrogen and the residue was reconstituted with acetonitrile/water (3:7, v/v). Chromatographic separation was done on a Phenomenex Luna 3 μm CN 100A column (50×3.0 mm) with a mobile phase consisting of acetonitrile/2 mM ammonium acetate (40:60, v/v) containing formic acid (0.1%, v/v) delivered using isocratic elution at a flow-rate of 0.25 mL/min. Analytes were detected by electrospray tandem mass spectrometry in the selective reaction monitoring mode over the clinically achievable range of 0.05–5 ng/mL. Quality control samples were assayed with each analytic run and were within 15% of the nominal concentration. The long-term plasma stability at −80°C was 209 days.

Pharmacokinetics:

A 1-compartment open linear population PK model derived from newborns with NAS receiving oral clonidine (19) was used to explore its goodness-of-fit to the available data using plasma concentrations of clonidine in 11 of the 12 infants with HIE during TH for which plasma clonidine levels were available for analysis. Of these 11 infants who had clonidine levels, 2 received IV clonidine (Q6h) during the cooling and rewarming phase, 1 received clonidine (Q6h) only during the cooling phase, and 8 received clonidine (Q8h) only during the cooling phase of TH. Using these levels and the aforementioned population PK model, PK parameters were re-estimated and the clearance and volume of distribution (standardized to a 70 kg adult) for IV clonidine were determined for the cohort of infants with HIE during TH. NONMEM v7.3 (Icon Development Solutions, Ellicott City, MD, USA) (20) was used for nonlinear mixed effect modeling, using PsN toolkit 3.4.2 (21) and Piraña version 2.8.0 (22) as modeling environment. First-order conditional estimation method with interaction (FOCE-I) was used for parameter estimation.

Four of the 12 infants who received clonidine and completed the study were administered clonidine Q6h. Because of variable autonomic instability in the first 4 infants, the medical safety monitor recommended the interval be increased to Q8h and to discontinue clonidine 4 hours prior to rewarming. Eight infants were then treated with Q8h dosing, and composite physiolgical data are presented on this Q8h cohort. PK data was obtained using plasma samples from a total of 12 infants of which 4 were treated Q6h and 8 were treated Q8h.

Statistical Analysis:

Data are presented as median and 25–75th percentile, unless otherwise stated. Graphs are presented as box and whisker plot, where the box is limited by the 25th and 75th percentiles and the solid line represents the median. For comparison between two groups, Mann-Whitney U test was used. For categorical values, χ^2 test was applied, and for continuous longitudinal variables (HR and BP), Wilcoxon test was used to compare pre-dose values with subsequent values. Significance was assigned by p-value ≤ 0.05 in all cases. Analysis was performed using IBM SPSS Statistics 24v (IBM Corporation, Armonk, NY).

RESULTS:

Study Subjects:

As outlined in the consort flow diagram (Fig 1), between March 13, 2013 and April 11, 2015 at the JHH NICU, 37 infants were diagnosed with perinatal depression, developed neonatal encephalopathy, and received treatment with whole body TH as per protocol. Of those, the parents of 10 infants were not approached due to severity of illness determined by the clinical team, which included the need for HFOV in 5 of them and diagnosis of persistent pulmonary hypertension of the newborn (PPHN) requiring iNO in 8 infants of which 4 required ECMO for stabilization. Need for iNO and ECMO had been predetermined to be exclusion criteria. Ultimately, 4 of the 10 infants whose parents were not approached died. Of the 27 infants eligible for enrollment, the parents of 14 declined to participate or were not approached due to unavailability of a team member to obtain consent (52%). Of the 13 infants whose parents signed informed consent, one infant did not receive the study drug due to worsening PPHN requiring iNO therapy and HFOV. In the end, 12 patients completed the study protocol: 4 infants received clonidine Q6h, of which 3 received clonidine in the cooling and rewarming phases of TH; the next 8 infants received clonidine Q8h, and the clonidine was discontinued 4 hours prior to rewarming. Demographic, perinatal, and outcome variables are detailed in Table 1 for all infants treated with clonidine; physiological data were available for all infants exposed to clonidine and clonidine plasma levels were available for the 12 infants.

For the historical control cohort (September 2013 to February 2014 and May 2015 to November 2015), clinically relevant variables for 48 infants were included in the database, of which 20 were excluded due to death (n=6), need for ECMO (n=7), need for inhaled NO and/or HFOV (n=7). Thus, a cohort of 28 infants were used as historical controls. Summative data for the total amount of morphine, core body temperature (CBT) during cooling phase of TH, time to rewarming are presented for historical control and clonidine (Q8h and Q6h) cohorts. The difference between medians was determined for the historical controls and infants exposed to clonidine Q8h.

Clonidine plasma levels:

A total of 29 clonidine levels from 11 infants were used in the PK analysis with a median of 3 (range 1–4) clonidine levels obtained per infant; 4 infants received clonidine Q6h (9 plasma levels) and 8 received clonidine Q8h (20 plasma levels). The infants received a median of 6 doses of clonidine (IQR 5–7). The group median plasma clonidine level

was 0.55 ng/mL (range 0.14–2.63 ng/mL); measured in samples obtained at a median of 7.9 hours (range 1–21 hours) after the previous dose of clonidine. For those who received clonidine Q6h, the median clonidine level was 0.63 ng/mL (range 0.38–1.16) and for those who received clonidine Q8h, the median clonidine level was 0.44 ng/mL (range 0.142–2.63). The estimated median volume of distribution (Vd) and clearance (CL) of IV clonidine (1 mcg/kg/Q6–8h) in infants with HIE during TH was 280 L (95% CI 131–475 L) and 11.89 L/hour (95% CI 8.57–18L), respectively, standardized to the body weight of a 70 kg adult.

Clonidine given Q8h during the cooling phase of TH did not cause physiologically significant changes in hemodynamic parameters.

In the first cohort of infants (n=4), clonidine was given Q6h during both the cooling and rewarming phase of TH. In this group of infants, 2/4 needed at least 1 dose of clonidine held or delayed during the cooling or rewarming phase because of bradycardia (HR < 80 after receiving clonidine) or hypotension (MAP ≤ 45mmHg); 1/4 infants required a fluid bolus at the start of the rewarming. One infant had an unexpected increase in blood pressure and persistently elevated HR, with a median HR of 140 bpm (range 132–163) throughout the cooling phase of therapeutic hypothermia, that was unresponsive to multiple doses of morphine in addition to the scheduled clonidine Q6h. Clonidine was administered throughout the cooling and rewarming phase and then weaned over 48 hours. During the rewarming phase, the infant's blood pressure did not decrease. During the weaning phase of the clonidine after rewarming, the infant was given 2 doses of hydralazine for systolic blood pressure 110 mmHg. An MRI on the 4th day of life was remarkable for extensive global HIE affecting the thalamus, dorsal putamina/globi pallidi, anterior pons, and lower brainstem. Because of the severity of the neurological injury, the parents elected to withdraw life-sustaining treatment on the 5th day of life; the infant died 4 days later. The death was immediately reported to the FDA and the Institutional Review Board as a serious adverse event, and the elevation of blood pressure with weaning of the clonidine requiring intervention was reported as an adverse event. The death was not deemed secondary to clonidine, and the study could continue. However, due to the episodes of hypotension or bradycardia in the other infants, the medical monitor recommended that the dosing interval be increased to Q8h.

In the second cohort of infants (n=8), the first dose of clonidine was given within 36 hours of starting TH, with subsequent doses given Q8h. Clonidine was discontinued ≥ 4 hours before the start of the rewarming. Heart rate decreased from a median (IQR) of 110 (104–114) to 101 (94–108) bpm 30 mins after the first dose of clonidine (p=0.03 vs baseline; Fig 2A). However, heart rate increased from median (IQR) of 106 (102–110) to 111 (104–122) bpm 30 mins after the second dose (p=0.02 vs baseline prior to second dose; Fig 2A). These two changes were not considered physiologically significant since the heart rate was always above 95 bpm and changes were not associated with changes in mean arterial blood pressure (MAP; Fig 2B) or systolic blood pressure (SBP; Fig 2C). Isolated changes in blood pressures were observed with the fourth dose of clonidine. Thirty minutes after the fourth dose of clonidine, MAP decreased from a median (IQR) of 58 (53–61) mmHg to 50 (45–56) mmHg (p=0.02 vs baseline prior to fourth dose; Fig 2B) and systolic blood pressure (SBP)

decreased from 73 (68–77) mmHg to 64 (57–71) mmHg (p=0.03; Fig 2C). These SBP and MAP measurements were within normal limits for full-term infants (23).

Five of 12 infants who received clonidine were also treated with dopamine prior to the first dose of clonidine with an infusion rate of 3, 2, 6, 5, and 11 mcg/kg/min, but were still eligible for enrollment. In 80% of the infants, the dopamine infusion rate was within ±3 mcg/kg/min of the starting dose throughout clonidine treatment with the exception of one subject, subject I. In subject I, the dopamine rate was increased from 6 to 12 mcg/kg/min from the second to the third dose of clonidine. An additional subject was treated with dopamine, 3 mcg/kg between the 1st and 3rd dose of clonidine, and discontinued before the 3rd dose. In 6 infants who did not receive dopamine at any time during clonidine treatment, HR, SBP, MAP, and DBP did not decrease, but had an upward trend with cumulative doses of clonidine

Clonidine administration was associated with decrease in “PRN” doses of opiates during TH.

Infants treated with clonidine (Q8h) received significantly less PRN morphine from the 1st to the 2nd day of life, requiring a median (IQR) of 0.12 (0.01–0.31 mg/kg) on the 1st day and only 0.02 (0–0.08) by the 2nd day of life (p< 0.001). Other than 1 infant who received a one-time dose of fentanyl on the first day of life, no other sedatives or analgesics were given. In comparison to the historical control group, infants treated with clonidine Q8h received 89% less PRN morphine for shivering or agitation during the second day of treatment (0.06 vs. 0.53 mg, p=0.001; Table 2).

Clonidine stabilized CBT in target temperature range during TH.

In infants treated with clonidine Q8h, 92.4% (90.4–93.0; median [IQR]) of the time during TH the CBT was within the target range (33–34ºC) with a maximum CBT of 34.1ºC, a minimum of 32.7ºC, and a change of only 1.3ºC during the 72 hours of hypothermia. When compared to the historical control group who only received morphine, infants treated with clonidine Q8h during TH spent 65% less time above 34°C (p=0.002; Fig 3B). Clonidine-treated infants spent 92% of the time in the optimal temperature range of 33–34°C, whereas control infants were within that range 79% of the time (p= 0.03, clonidine vs control; Fig 3C). Similarly, temperature deviations from the therapeutic range were less prominent in the infants treated with clonidine, who had a maximum temperature of 34.1°C vs 34.4°C in controls (Figure 3D, p=0.005) and a temperature delta change of 1.3°C vs 2.0°C in controls (Figure 3F, p=0.009). When passively increasing the temperature set point by 0.5°C every 30 mins to reach normal body temperature, infants treated with clonidine took 48% longer than control infants to reach CBT of 36°C (8.7 vs. 5.9 hours, p=0.007 clonidine vs control).

DISCUSSION:

The major findings from this prospective study is that IV clonidine (1 mcg/kg Q8h over 30 mins) during the cooling phase of TH was not associated with acute adverse cardiovascular events, and was associated with (1) less opiate given “as needed” for shivering or agitation over time, (2) stability of CBT in the optimal target range during TH, and (3) reduced

clonidine clearance by 21.8% with a volume of distribution that was 28.4% less than predicted from the population PK model derived from data obtained in term infants with NAS.

The impetus for this study was two-fold: (1) the observation in our NICU that many infants undergoing TH would shiver and become agitated, necessitating escalating doses of opiates, which, in some infants, was associated with respiratory depression requiring increasing levels of respiratory support; and (2) maintaining CBT in the optimal therapeutic range is challenging since hypothermia induces intense counter-regulatory defenses such as shivering and non-shivering thermogenesis (24). The counter-regulatory defenses increase stress and agitation thereby decreasing the effectiveness of the TH. Thus, we sought to exploit the pharmacological properties of an α_2-receptor agonist using IV clonidine, which causes sedation and decreases counter-regulatory thermogenic defenses by blocking central α_2-receptors leading to decreased sympathetic output (25, 26). Metabolism and clearance of many drugs are altered in patients with HIE due to end-organ injury and the effects of TH. In adults and older children, the bioavailability of clonidine has been reported at 75–100% and 100% via rectal and epidural routes, respectively (27–29). Fifty percent of clonidine is excreted unchanged in the urine, and, in adults, renal insufficiency significantly prolongs its clearance (28).

Clonidine formulated specifically for IV use is not approved in the US, but is available in Europe where it is used for sedation in ICU patients. In a study conducted in the United Kingdom, continuous infusion of IV clonidine (1.0–2.0 mcg/kg/h) was well tolerated without cardiovascular side effects in 30 ventilated infants and children ≤ 10years of age of which 10 were postoperative from cardiovascular surgery (30). These infants and children received 8–16 times the dose used in our infants with HIE during TH. However, clonidine levels were not measured (30). Here, we report the first description of administering IV clonidine (formulated for epidural use) to patients in the US, and describe the PK of IV clonidine in infants with HIE during TH.

For comparison, the most comprehensive published population PK study of clonidine in neonates was performed in infants being treated with oral clonidine 1 mcg/kg Q4h for NAS during the first weeks of life (19). In these infants, the distribution of clonidine best fit a 1-compartment PK model with a median volume of distribution (Vd/F) of 402 L/70 kg (95% confidence interval [CI] 255–581 L) and clearance (CL/F) of 15.2 L/hour/70 kg (95% CI 11.4–17.7). We hypothesized that babies with HIE during TH would have lower clearance than the infants with NAS because of renal injury and TH. Thus, we started clonidine at interval dosing of Q6h in this HIE population instead of the Q4h that was used in infants with NAS. Due to hemodynamic instability in the infants who received clonidine Q6h, we further extended the interval to Q8h. We assume the bioavailability of oral clonidine is 100% (F=1) for neonates, the CL/F for infants receiving oral clonidine would be 15.2 L/hour/70 kg (15.2 L/hour * 1) compared to 11.89 L/hour/70 kg in infants with HIE during TH, and the Vd/F would be 402 L/70 kg (402 L * 1) with oral administration in NAS infants compared to 280.43 L/70 kg in infants with HIE during TH. These estimates suggest the clearance and volume of distribution of clonidine in infants with HIE during TH are reduced by 21.8% and 28.4%, respectively. Given the uncertainty in bioavailability in the neonatal population, we

caution the inference of lower clearance and volume of distribution in HIE babies as we are not able to confirm this given our small sample size.

Cumulative dose of clonidine was not associated with hypotension. Plasma levels were 0.68 ± 0.1 ng/mL, and 0.58 ± 0.12 (mean ± SD), for the entire cohort and for infants who received clonidine Q8h, respectively. These levels are similar to clonidine levels (0.3–0.8 ng/mL) that were achieved with oral clonidine for pre-operative sedation in children (31), but are less than the mean plasma level (1.38 ng/mL, 95% CI 1.0–1.8) that was associated with adequate sedation in a pediatric intensive care unit (PICU) population with only respiratory failure. The PICU study population had a median age of 3 months and was given oral clonidine (3–5 mcg/kg Q8h) (32). The plasma levels reported in both studies (31, 32) using oral clonidine were also not associated with significant changes in heart rate or blood pressure.

Contrary to what we expected, cumulative doses of clonidine was associated with a trend toward an increase in blood pressure. Clonidine can bind to peripheral α_1-receptors causing transient hypertension (28, 33). Moreover, in pre-clinical models of sepsis with acute kidney injury, catecholamine levels are often high and associated with catecholamine-resistant hypotension. Clonidine administration at clinically relevant doses in these preclinical models increased blood pressure either by increasing cardiac output or vasoconstriction with higher doses of clonidine associated with higher levels of vasopressin (34). Infants with asphyxia exhibit similar physiological derangements: high levels of catecholamine (35) and catecholamine-resistant hypotension with acute kidney injury. We did not measure vasopressin in our infants, so we do not know if the trend toward higher blood pressure was associated with increasing vasopressin levels. The infant who had persistent tachycardia and elevated blood pressure, both unresponsive to clonidine and multiple doses of morphine, was, however, an outlier. This infant had significant cerebral edema detected on ultrasound within the first 6 hours of life. We believe injury to the vasomotor system in the brainstem may have contributed to this unusual response. Paroxysmal hypertension and tachycardia is well described in individuals with traumatic brain injury and cerebral edema (36).

Maintaining and stabilizing CBT during TH is highly desirable to deliver effective treatment, thus adjunct therapies that would create thermal tolerance to hypothermia could be beneficial. Several classes of drugs increase thermal tolerance including volatile anesthetics, opiates, meperidine (37), and central α_2-adrenergic agonists such as clonidine and dexmedetomidine (38). α_2-adrenergic agonists create tolerance to hypothermia by binding to α_2-adrenergic heteroreceptors on excitatory premotor sympathetic neurons in the brain and inhibiting norepinephrine release from sympathetic ganglia involved in shivering and non-shivering thermogenesis (39). Clonidine reduces the shivering and vasoconstriction threshold in adults (37, 38), reduces shivering in infants with HIE undergoing TH (40), and reduces post-surgical shivering in children and adults (24, 41). Dexmedetomidine, another α_2-adrenergic agonist commonly used for sedation in intensive care settings, is also effective in inducing thermal tolerance (38). A single center retrospective study published in 2018 described their experience using dexmedetomidine for sedation in 19 infants with HIE during therapeutic hypothermia who tolerated the drug without significant cardiovascular instability (42). A 2020 publication reports the pharmacokinetics of dexmedetomidine in

7 infants with HIE during TH (15) who also tolerated it well. At the time our study started enrollment in 2013, published experience using dexmedetomidine in children was sparse and included case reports of significant side effects (43) and preclinical studies in piglet models of HIE during TH described profound cardiovascular instability and 10-fold reduction of clearance of dexmedetomidine (44). Thus, we chose clonidine because of its pharmacological properties in inducing thermal tolerance and reducing shivering. Moreover, it (1) is an effective sedative with minimal effect on respiratory drive (26), (2) has a good safety profile in infants and children (13), (3) can be given by IV and orally, and (4) was well tolerated in our previous cohort of term infants at a similar postnatal age who received clonidine for detoxification from opiates (14).

Clonidine did stabilize CBT with infants spending less than 5% of the time during TH above or below target temperature (33.5 ± 0.5°C). We also noted that those infants who were treated with clonidine on average took 48% longer to rewarm than infants with a similar level of illness who were only treated with morphine (~9 vs 6 hours, respectively). The protocols and equipment were the same in the clonidine group and the group of historical controls who only received morphine, suggesting that clonidine in infants with HIE is much more effective than morphine in achieving tolerance to hypothermia. Less temperature fluctuations during TH is associated with better MRI findings as reported by Brotschi et al. (45).

Similar to what has been described for adults and older children, clonidine is opiate sparing; we show that clonidine by the 2nd day of treatment effectively reduced the need for opiates for agitation during TH, which was 87% less than the PRN doses given to infants in the historical controls on the 2nd day of TH who received scheduled Q6h morphine. One limitation in interpreting these data is that we did not have a standard algorithm for opiate administration in the clonidine-treated or historical control group. We tried to minimize this limitation by selecting a historical control group that straddled the period of the clonidine study with little changes in clinical practice.

We did not use a sedation scale in this study since our initial intent was to use shivering and not sedation as a secondary outcome variable. To that end, we attempted to use the validated bedside shivering scale, designed for adults by Badjatia et al. (38), that characterizes shivering using a 4-point scale, but we were unable to apply this scale to our infants. In our infants, the legs and arms were tightly flexed with gross movements of the upper and lower extremities, and the infants appeared uncomfortable. Infants who are agitated have similar movements, thus making it difficult to distinguish between shivering versus agitation/pain. Although it is routinely taught that infants use only non-shivering thermogenesis during hypothermia, a subset of infants who undergo TH for HIE do shiver. While it is unclear if shivering is symptomatic of pain or discomfort, infants in our NICU were given opiates for “shivering” as it makes the target temperature during TH more difficult to maintain. Therefore, at the time of the study in the NICU at Johns Hopkins, opiate administration was the “standard of care.” In addition to their effectiveness in reducing shivering, α_2-adrenergic receptor agonists may also confer neuroprotection in newborn models of HIE (46), and other models of neurological injury (47) that may be of added benefit.

Limitations of study design and interpretation:

Our study was designed to accomplish two goals: (1) to determine the short-term safety of a dose of clonidine that would be well tolerated in infants with HIE undergoing TH without significant adverse cardiovascular events; and (2) to determine the pharmacokinetics of clonidine in this limited population. The design allowed us to accomplish these goals, but had several limitations because of the small sample size. We cannot precisely describe the relationship between systemic blood pressure and cerebral autoregulation as we have previously done in a cohort of infants with HIE during cooling and rewarming who only received morphine for sedation (48, 49). Nor are we able to characterize the pharmacodynamics of clonidine, the relationship between clonidine levels and physiological variables, or its effect on neuroprotection and long-term outcome. However, these studies can be designed now that we have established a safe, tolerable dose of clonidine and method of administration in this population.

In summary, our data show that clonidine can be used safely in infants with HIE being treated with TH; clonidine optimizes sedation and stabilizes temperature during TH. Our data are generalizable to infants with HIE receiving TH and suggest that in this population clonidine may be an acceptable adjunct or alternative to opiates in order to mitigate the known side-effects associated with high doses: excessive sedation, respiratory depression, decreased GI motility, and delay in feeding readiness.

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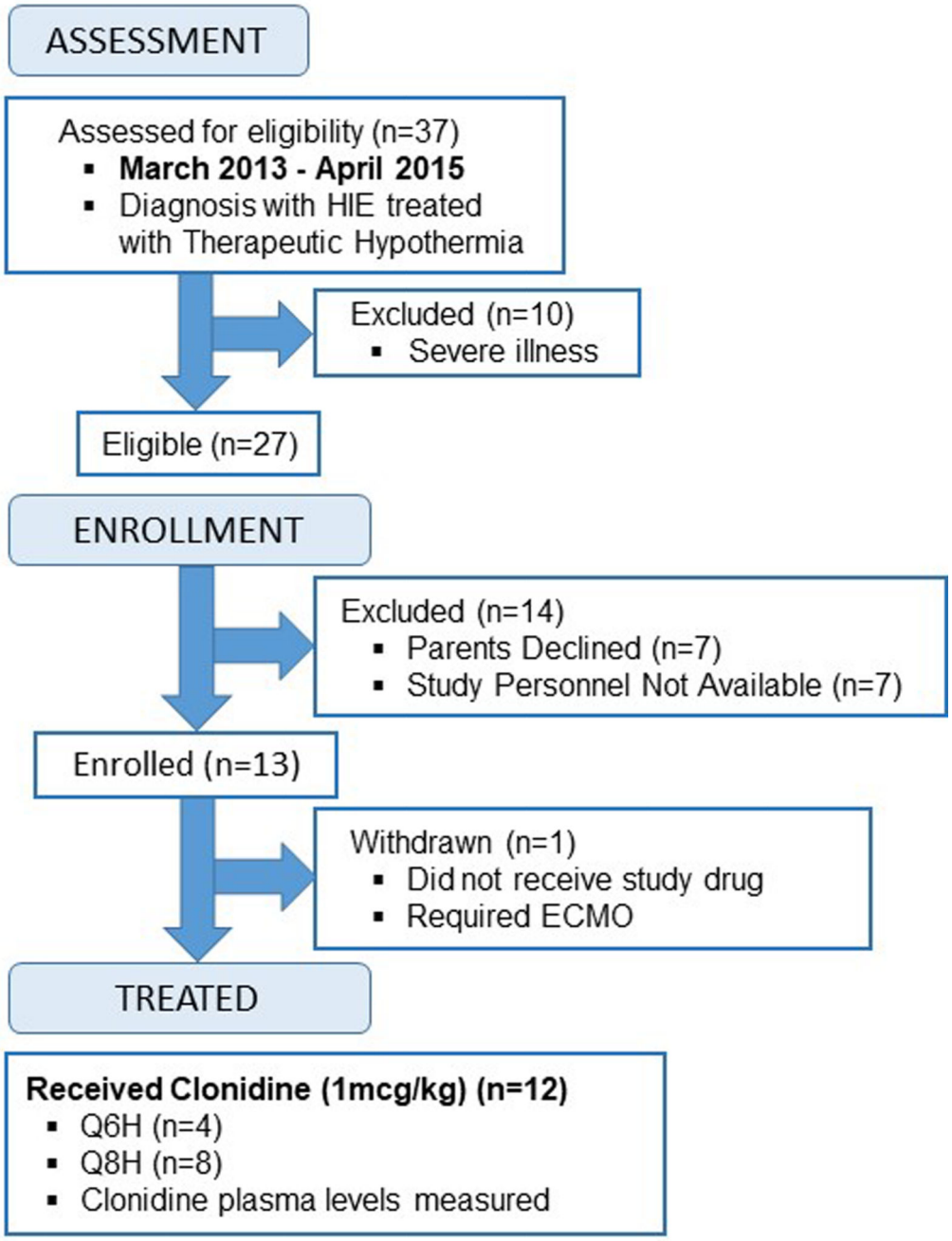

Figure 1:
Consort diagram.

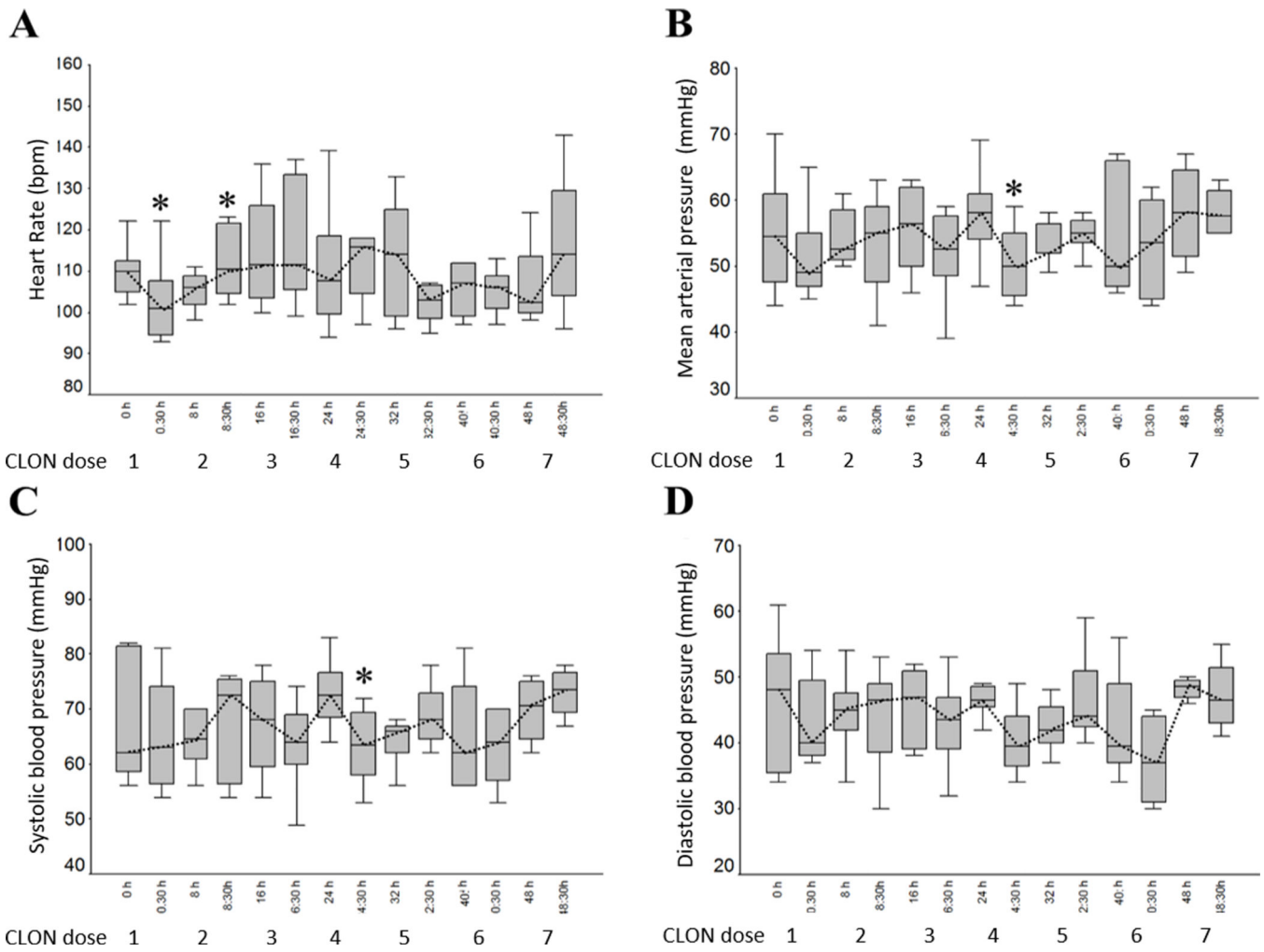

Figure 2. Effect of clonidine on heart rate and blood pressure.

Comparisons were made between the heart and blood pressure prior to each subsequent dose and 30 mins after the dose of clonidine for infants who received clonidine Q8h. Only minor and isolated changes were observed which were not sustained. Heart rate decreased from baseline 30 mins after the 1st dose and increased 30 mins after the 2nd dose from baseline (A). Mean arterial (B) and systolic blood pressure (C) significantly decreased from baseline only after the 4th dose of clonidine, which was not associated with a significant decrease in diastolic blood pressure (D) or heart rate. Values are Median IQR, * Mann-Whitney U; * $p<0.05$, 30 mins after clonidine vs baseline prior to the dose.

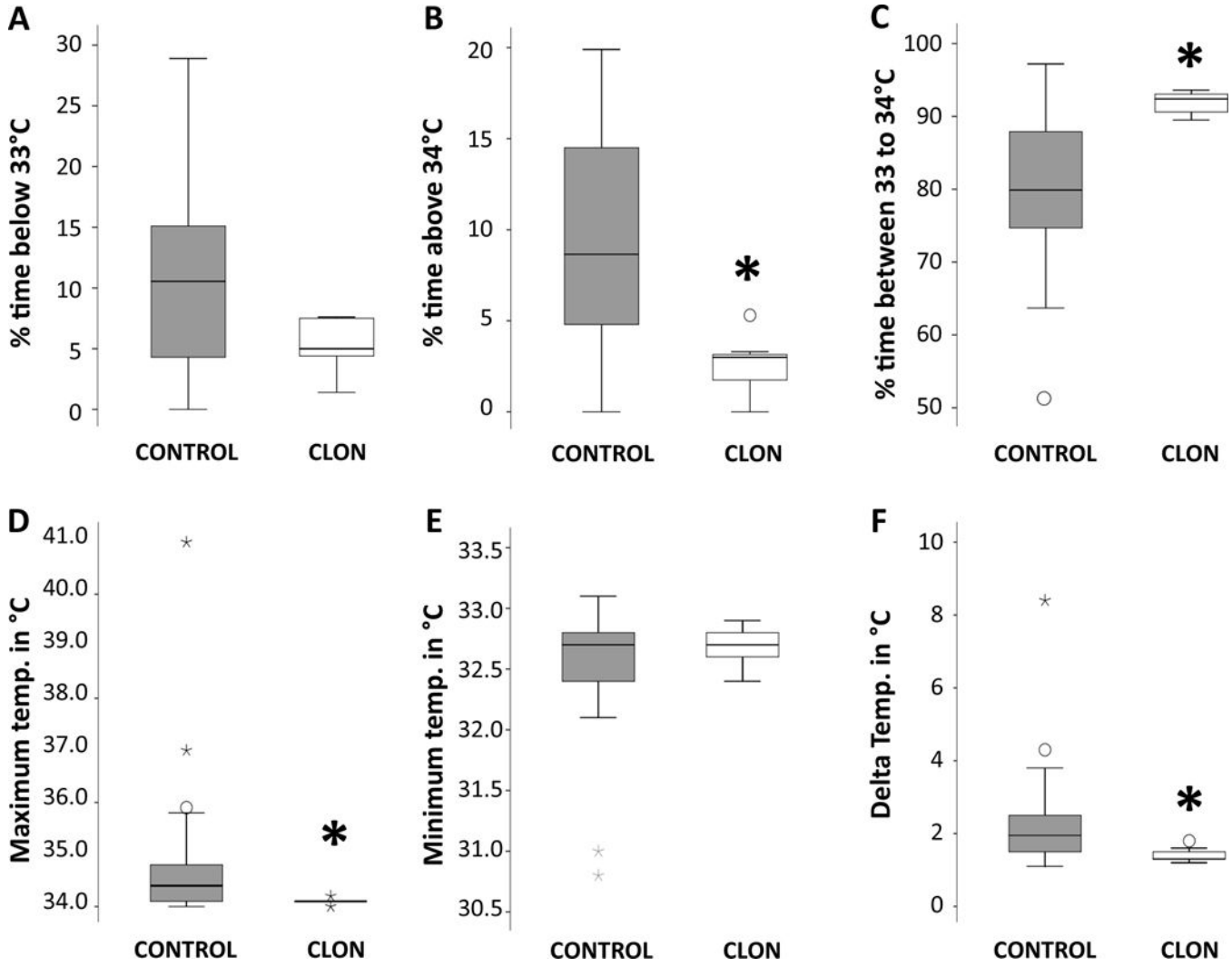

Figure 3. The effect of clonidine on Core Body Temperature (CBT) during the cooling phase of TH.

The percent of time below 33°C in infants treated with clonidine Q8h was similar to historical controls (A). Infants treated with clonidine (1) spent less time during TH above 34°C (B); (2) spent more time in the target range between 33 to 34°C (C); (3) had lower maximum CBT (D); and (4) had fewer fluctuations in CBT (F) than control infants. Values are Median IQR, Mann-Whitney U; * $p<0.05$ vs control infants.

TABLE 1 -

DEMOGRAPHICS, PERINATAL AND OUTCOME VARIABLES

VARIABLE	CONTROL (n= 28)	CLON Q6h (n=4)	CLON Q8h (n=8)
GA, wk (median, IQR)	39.4 (37.2–40.2)	39.3 (37.7–39.5)	36.7 (35.5–39.1) *
Gender, male % (n)	71% (20)	50% (2)	50% (4)
BW, gr (median, IQR)	3180 (2736–3662)	2935 (2520–3425)	2895 (2488–3595)
Race, Black % (n)	32% (9)	25 % (1)	38 % (3)
STAT C-section, % (n)	50% (14)	75% (3)	63% (5)
NRFHT, % (n)	64% (18)	75% (3)	75% (6)
PEC, % (n)	18% (5)	0% (0)	25% (2)
Cord/placenta event, % (n)	39% (11)	75% (3)	50% (4)
Apgar 1min, (median, IQR)	1 (1–2)	1 (1–2)	1 (0–2)
Apgar 5min, (median, IQR)	4 (3–5)	2 (2–3)	5 (3–7)
Apgar 10min, (median, IQR)	5 (4–7)	5 (3–6)	6 (6–7)
Cord/1st BG pH (median, IQR)	6.95 (6.86–7.11)	6.95 (6.70–7.04)	7.05 (6.93–7.09)
Cord/1st BG BD (median, IQR)	15 (9–18)	15 (12–21)	16 (8–18)
Cerebral edema by HUS, % (n)	56% (15)	50% (2)	50% (4)
Passive cooling, % (n)	64% (18)	75% (3)	50% (4)
TH initiation, hr (median, IQR)	4.1 (3.2–4.4)	3.5 (2–4)	2 (0.3–4.8)
1st Glucose, mg/dl (median, IQR)	111 (74–122)	58 (49–74)	100 (89–111)
1st INR, (median, IQR)	1.7 (1.3–2.2)	1.8 (1.5–2.5)	1.8 (1.3–2.1)
1st aPTT, sec (median, IQR)	17 (13.7–22.1)	18.5 (15.8–24.6)	18 (13.9–21.6)
Time to PO, days (median, IQR)	8 (6–10)	8 (6–8)	9 (7–15)
Mech. vent, days (median, IQR)	1 (1–4)	2 (0–7)	1 (0–3)
Time to RW, hrs (median, IQR)	5.9 (5–7)	9.9 (8.2–12.2)	8.7 (7.4–10.1) *

BD, base deficit; **BG**, blood gas; **BW**, birth weight; **CLON**, clonidine; **C-section**, cesarean section; **GA**, Gestational age; **HUS**, head ultrasound; **IQR**, interquartile range; **Mech. Vent.**, mechanical ventilation; **NRFHT**, non-reassuring fetal heart tracing; **PEC**, pre-eclampsia; **PO**, per os; **RW**, rewarm; **TH**, therapeutic hypothermia **Cord/ placenta events include: placenta previa, abruption placentae, and cord prolapse**

*, $p \leq 0.05$ (control compared to Q8h clonidine-treated group)

TABLE 2.

MORPHINE EXPOSURE DURING THERAPEUTIC HYPOTHERMIA

	CONTROL (n= 28)	CLON Q6h (n=4)	CLON Q8h (n=8)	p-value
DOL 1 Total (mg/24hr)	0.80 (0.61–0.98)	0.60 (0.12–1.03)	0.34 (0.05–1.02)	0.08[a]
DOL 2 Total (mg/24hr)	0.78 (0.68–1.05)	0.16 (0.04–0.29)	0.06 (0–0.18)	<0.001[a]*
DOL 1, Q6h Total (mg/kg/24hr)	0.06 (0.05–0.08)	0.05 (0.01–0.08)	0.03 (0–0.08)	0.05[a]*
DOL 2, Q6h Total (mg/kg/24hr)	0.06 (0.05–0.08)	0.01 (0.00–0.02)	0.01 (0–0.02)	<0.001[a]*
DOL 1, PRN Total (mg/24hr)	0.49 (0.37–0.75)	0.60 (0.1–1.03)	0.34 (0.05–1.02)	0.30[a]
DOL 2, PRN Total (mg/24hr)	0.53 (0.40–0.82)	0.16 (0.04–0.29)	0.06 (0–0.18)	0.001[a]*
DOL 1, PRN Total (mg/kg/24hr)	0.17 (0.12–0.23)	0.20 (0.05–0.32)	0.12 (0.01–0.31)	0.44[a]
DOL 2, PRN Total (mg/kg/24hr)	0.17 (0.12–0.22)	0.05 (0.01–0.09)	0.02 (0–0.08)	0.001[a]*

*, $p \leq 0.05$;

[a], Mann-Whitney U Test comparing CLON Q8h vs Control

CLON, clonidine; **DOL**, day of life; **Eq**, equivalent; **IQR**, Interquartile range; **PRN**, pro re nata