scientific reports

Check for updates

OPEN

Methylxanthine use in infants with hypoxic-ischemic encephalopathy: a retrospective cohort study

Madeleine E. Laughon[1,4], Jacob K. Johnson[1,4], Rachel G. Greenberg[2], Reese H. Clark[3] & Wesley M. Jackson[1]✉

Therapeutic hypothermia is the standard treatment for hypoxic-ischemic encephalopathy (HIE), but despite its widespread use, the rates of mortality and neurodevelopmental impairment for moderate to severe HIE remain around 30%. Methylxanthines, such as caffeine and aminophylline, have potential neuroprotective effects in the setting of hypoxic-ischemic injury. However, data on the safety and efficacy of methylxanthines in the setting of therapeutic hypothermia for HIE are limited. This retrospective multicenter study examined in-hospital outcomes in 52 infants with HIE receiving methylxanthines and therapeutic hypothermia. The frequency of mortality and in-hospital morbidities were similar to those of infants enrolled in clinical trials undergoing therapeutic hypothermia without adjunctive therapies. Clinical trials of methylxanthines for neuroprotection in HIE are needed to determine safety and efficacy and should explore optimal dosing and timing of methylxanthine administration.

Therapeutic hypothermia is the standard treatment for hypoxic-ischemic encephalopathy (HIE), but despite its widespread use, the rates of mortality and neurodevelopmental impairment for moderate to severe HIE remain around 30%[1]. To address this, neonatologists are exploring adjunctive therapies to further improve outcomes. Preclinical studies suggest methylxanthines, such as caffeine and aminophylline, have potential neuroprotective effects in the setting of hypoxic-ischemic injury[2,3]. Mechanisms by which methylxanthines may offer neuroprotection are a reduction in neuronal cell death and anti-inflammatory and anti-oxidative properties which protect against the cascade of injuries following reperfusion[4,5]. Furthermore, methylxanthines may protect against acute kidney injury (AKI) associated with HIE, and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend a single dose of theophylline for HIE-related AKI[6,7]. Data on the safety and efficacy of combining therapeutic hypothermia with methylxanthines in infants with HIE is limited to a few small studies[8,9]. We evaluated in-hospital outcomes for infants with HIE exposed to concomitant use of methylxanthines and hypothermia.

Methods

We obtained data from the Pediatrix Medical Group Clinical Data Warehouse, encompassing clinical information from > 300 neonatal intensive care units[10]. We included inborn infants who received therapeutic hypothermia for HIE on postnatal day 0 or 1, received methylxanthines (caffeine or aminophylline) on postnatal day 0–3, and were discharged between 2007 and 2020. We excluded infants with major congenital anomalies. Other data included prenatal characteristics, demographics, medication exposures, in-hospital clinical outcomes, and length of hospital stay. Neuroimaging data were not available for inclusion in this analysis. We performed a literature review of therapeutic hypothermia clinical trials to compare outcomes to this population, if available.

Definitions

We examined the day of initiation and duration of methylxanthine exposure for each infant. We examined creatinine rise > 0.3 mg/dL over 2 days during the first postnatal week per KDIGO criteria[11], prothrombin time

[1]Department of Pediatrics, UNC School of Medicine, The University of North Carolina at Chapel Hill, Campus Box #7596, Chapel Hill, NC 27599-7596, USA. [2]Department of Pediatrics, Duke University, Durham, NC, USA. [3]Pediatrix Center for Research, Education, Quality, and Safety, Sunrise, FL, USA. [4]These authors contributed equally: Madeleine E. Laughon and Jacob K. Johnson. ✉email: wesley.jackson@unc.edu

(PT) > 16 s, aspartate aminotransferase (AST) > 200 U/L and alanine aminotransferase (ALT) > 100 U/L[12,13], and mechanical ventilation for ≥ 5 days. We identified exposures to anti-epileptic drugs (AEDs) and examined gastrostomy tube placement prior to discharge.

Statistical analysis

We used standard summary statistics to describe study variables and performed comparisons among infants exposed to only one methylxanthine using Fisher's exact or Wilcoxon rank sum tests. The use of de-identified data was approved with waiver of consent by the Duke University Health System Institutional Review Board (IRB). The study was performed in accordance with the relevant guidelines and regulations and in accordance with the Declaration of Helsinki.

Results

Among 5909 infants with HIE receiving therapeutic hypothermia between 2007 and 2020, 52 (0.9%) received methylxanthine therapy. Twenty-eight infants received caffeine only, 22 received aminophylline only, and two who received both drugs were included in summary statistics for both cohorts. Four infants (14%) in the caffeine group and 4 infants (20%) in the aminophylline group died, while 10% of infants not exposed to methylxanthines died (Table 1). Infants receiving aminophylline were born at slightly later gestational age (median 38 weeks [25th–75th percentile: 38–39] vs. 36 weeks [35–39]; $p = 0.06$) and had larger birth weight (3.25 kg [2.54–3.60] vs. 2.77 kg [2.12–3.38]; $p = 0.03$) than caffeine recipients. Caffeine treatment ranged from 1 to 18 days, while aminophylline treatment ranged from 1 to 4 days. There were no statistically significant differences in incidence of renal failure (41% vs. 19%; $P = 0.18$) or median peak creatinine levels (1.3 mg/dL [0.9–1.7] vs. 1.0 mg/dL [0.7–1.3]; $P = 0.06$) in aminophylline-treated infants compared to caffeine-treated infants. There were no significant differences in median baseline creatinine in the caffeine (0.85 mg/dL), aminophylline (0.91 mg/dL), and no methylxanthine (0.90 mg/dL) groups ($P = 0.38$). The aminophylline and caffeine groups had a similar frequency of AED exposure in the first postnatal week (42% vs. 37%; $P = 0.77$).

Discussion

Previous studies investigating methylxanthines in the setting of HIE have primarily focused on kidney outcomes. A meta-analysis of six trials (n = 436) conducted in term infants with severe birth asphyxia in settings which did not have therapeutic hypothermia available found that a prophylactic dose of theophylline reduced AKI incidence compared to placebo without increasing mortality or seizures[14]. A retrospective study of 16 infants with HIE receiving therapeutic hypothermia found that early aminophylline use was associated with increased urine output and lower serum creatinine[8]. Finally, a prospective, open-label trial of caffeine in 17 infants with HIE

Outcome	Caffeine group (n = 30)	Aminophylline group (n = 24)	No methylxanthine group (n = 5857)	Hypothermia alone in trials (if available)
Death—% (no. infants)	14 (4/28)	20 (4/20)	10 (557/5443)	7–29[12,13,15–17]
Length of hospital stay—days				
Median	20	16	14	12–20[12,13,17]
5th–95th percentiles	8–45	8–31	8–46	–
Feeding—% (no. infants)				
Gastrostomy tube placement	7 (2/30)	0 (0/24)	6 (347/5857)	7–9[12,13,17]
Hepatic—% (no. infants)				
Coagulopathy (PT > 16 s)	91 (10/11)	86 (18/21)	80 (2612/3260)	41[13]
Hepatic Dysfunction (AST > 200 U/L and ALT > 100 U/L)	39 (7/18)	40 (8/20)	39 (1693/4298)	20–47[12,16,17]
Neurologic—% (no. infants)				
Received AED in first postnatal week	37 (11/30)	42 (10/24)	44 (2565/5857)	44–80[12,16]
Received > 1 AED in first postnatal week	13 (4/30)	13 (3/24)	10 (561/5857)	–
Pulmonary—% (no. infants)				
Receiving mechanical ventilation for ≥ 5 days	23 (7/30)	29 (7/24)	26 (1530/5857)	16[17a]
Renal				
Creatinine rise > 0.3 mg/dL in 2-day period—% (no. infants)	19 (4/21)	41 (9/22)	15 (601/4134)	10[17b]–65[16c]
Peak creatinine				
Median	1.00	1.25	0.91	–
5th–95th percentiles	0.63–1.78	0.65–3.01	0.51–1.93	–

Table 1. In-hospital mortality and morbidities in infants with HIE who received methylxanthines. *PT* Prothrombin time; *AST* Aspartate aminotransferase; *ALT* Alanine transaminase; *AED* Anti-epileptic drug. [a]Defined as > 7 days mechanical ventilation. [b]Defined as serum creatinine rise ≥ 1.5 × baseline. [c]Defined as serum creatinine > 1 mg/dL.

receiving therapeutic hypothermia at a single center found an 18% incidence of AKI with frequencies of mortality and seizures similar to those reported in the intervention arm of the Whole-Body Hypothermia for HIE trial[9,12].

The current study provides further insights into methylxanthines use in infants with HIE undergoing therapeutic hypothermia. The frequency of mortality and morbidities were similar to those of infants undergoing therapeutic hypothermia without adjunctive therapies in clinical trials[12,13,15–17]. Of note, the most recent clinical trials demonstrated lower mortality in the standard hypothermia arm compared to earlier trials, likely due to the widespread implementation of hypothermia as the standard of care for treating HIE[15,17]. While inconsistent definitions of renal failure across studies make direct comparisons challenging, a large cohort study utilizing a similar definition as our study found a frequency of AKI in 38% of infants receiving hypothermia for HIE[18]. Because the precise timing of methylxanthine administration in our population is not known, we were not able to report whether the medication was administered soon after delivery as recommended by the KDIGO guidelines[6]. While we are unable to determine the indication for methylxanthine use in this dataset, the shorter duration of aminophylline use and the higher peak creatinine in the aminophylline group compared to the caffeine group may reflect a decision by the clinician to use aminophylline for AKI prevention or treatment, while caffeine may have been used for respiratory support to prevent or treat apnea. The increase in mortality and length of stay in the methylxanthine group compared to infants who did not receive methylxanthines likely reflects confounding by indication whereby infants with more severe disease may have been more likely to receive the intervention.

Considering caffeine's association with a reduced seizure threshold and the FDA label's mention of seizures as a potential side effect of caffeine overdose, we explored AED receipt as a proxy for clinical seizures and found that AED exposures were similar to those reported in trials[19,20]. While our study leveraged observational data from an extensive clinical database, shedding light on methylxanthine administration during therapeutic hypothermia for HIE, some limitations must be acknowledged. Most importantly, we were not able to capture MRI brain results from the database in infants exposed to methylxanthines. Studies investigating the therapeutic utility of methylxanthines in the setting of HIE will need to include neuroimaging and neurodevelopmental follow up data. Missing data and infant transfers limited our ability to ensure complete outcome uniformity. In addition, the uncertainty in dosing, timing, and indication of caffeine and aminophylline administration in our study limits our ability to draw conclusions on the utility of methylxanthines in the setting of HIE.

Conclusion

Methylxanthines have potential neuroprotective effects in the setting of HIE. In this retrospective study of infants exposed to methylxanthines and therapeutic hypothermia, we found that in-hospital mortality and morbidities were similar to those described in trials of infants receiving therapeutic hypothermia alone. Clinical trials are needed to ascertain the safety and efficacy of methylxanthines in infants undergoing therapeutic hypothermia for HIE.

Data availability

The data that support the findings of this study are available from the Pediatrix Medical Group but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Pediatrix Medical Group. The corresponding author may be contacted for any requests for data.

Received: 9 April 2024; Accepted: 16 August 2024
Published online: 17 August 2024

References

1. Shankaran, S. *et al.* Effect of depth and duration of cooling on death or disability at age 18 months among neonates with hypoxic-ischemic encephalopathy: A randomized clinical trial. *JAMA* **318**(1), 57–67 (2017).
2. Bruschettini, M., Moreira, A., Pizarro, A. B., Mustafa, S. & Romantsik, O. The effects of caffeine following hypoxic-ischemic encephalopathy: A systematic review of animal studies. *Brain Res.* **1790**, 147990 (2022).
3. Sabir, H. *et al.* Comparing the efficacy in reducing brain injury of different neuroprotective agents following neonatal hypoxia-ischemia in newborn rats: A multi-drug randomized controlled screening trial. *Sci. Rep.* **13**(1), 9467 (2023).
4. Kilicdag, H., Daglioglu, Y. K., Erdogan, S. & Zorludemir, S. Effects of caffeine on neuronal apoptosis in neonatal hypoxic-ischemic brain injury. *J. Matern. Fetal Neonatal Med.* **27**(14), 1470–1475 (2014).
5. Di Martino, E. *et al.* Defining a time window for neuroprotection and glia modulation by caffeine after neonatal hypoxia-ischaemia. *Mol. Neurobiol.* **57**(5), 2194–2205 (2020).
6. Khwaja, A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin. Pract.* **120**(4), c179-184 (2012).
7. Segar, J. L., Chock, V. Y., Harer, M. W., Selewski, D. T. & Askenazi, D. J. Fluid management, electrolytes imbalance and renal management in neonates with neonatal encephalopathy treated with hypothermia. *Semin. Fetal Neonatal Med.* **26**(4), 101261 (2021).
8. Chock, V. Y., Cho, S. H. & Frymoyer, A. Aminophylline for renal protection in neonatal hypoxic-ischemic encephalopathy in the era of therapeutic hypothermia. *Pediatr. Res.* **89**(4), 974–980 (2021).
9. Jackson, W., Gonzalez, D., Greenberg, R. G., Lee, Y. Z. & Laughon, M. M. A phase I trial of caffeine to evaluate safety in infants with hypoxic-ischemic encephalopathy. *J. Perinatol.* https://doi.org/10.1038/s41372-023-01752-y (2023).
10. Spitzer, A. R., Ellsbury, D. & Clark, R. H. The pediatrix babysteps (R) data warehouse–a unique national resource for improving outcomes for neonates. *Indian J. Pediatr.* **82**(1), 71–79 (2015).
11. Selewski, D. T. *et al.* Neonatal acute kidney injury. *Pediatrics* **136**(2), e463-473 (2015).
12. Shankaran, S. *et al.* Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N. Engl. J. Med.* **353**(15), 1574–1584 (2005).
13. Azzopardi, D. V. *et al.* Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N. Engl. J. Med.* **361**(14), 1349–1358 (2009).
14. Bhatt, G. C., Gogia, P., Bitzan, M. & Das, R. R. Theophylline and aminophylline for prevention of acute kidney injury in neonates and children: A systematic review. *Arch. Dis. Child.* **104**(7), 670–679 (2019).

15. Shankaran, S. *et al.* Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: A randomized clinical trial. *JAMA* **312**(24), 2629–2639 (2014).
16. Gluckman, P. D. *et al.* Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. *Lancet* **365**(9460), 663–670 (2005).
17. Wu, Y. W. *et al.* Trial of erythropoietin for hypoxic-ischemic encephalopathy in newborns. *N. Engl. J. Med.* **387**(2), 148–159 (2022).
18. Selewski, D. T., Jordan, B. K., Askenazi, D. J., Dechert, R. E. & Sarkar, S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. *J. Pediatr.* **162**(4), 725-729.e721 (2013).
19. van Koert, R. R., Bauer, P. R., Schuitema, I., Sander, J. W. & Visser, G. H. Caffeine and seizures: A systematic review and quantitative analysis. *Epilepsy Behav* **80**, 37–47 (2018).
20. Caffeine Citrate Label. [cited]Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20793s1lbl.pdf

Author contributions

M.E.L., J.K.J., R.G.G., R.H.C., and W.M.J. participated actively in drafting sections of the manuscript, editing, and approving the final submitted version.

Funding

This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development grant K23HD111623 to Dr. Jackson.

Competing interests

MEL, JKJ, RHC, and WMJ have no conflicts of interest to disclose. RGG has received support from industry for research services (https://dcri.org/about-us/conflict-of-interest/).

Additional information

Correspondence and requests for materials should be addressed to W.J.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.