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Should neonates with perinatal asphyxia receive a single dose of IV Theophyline to prevent acute kidney injury?

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Perinatal asphyxia is a common reason for admission to a neonatal intensive care unit and is frequently associated with encephalopathy and multi-organ dysfunction.(1) Acute kidney injury (AKI) occurs commonly in critically ill neonates and is associated with adverse outcomes (2). In the cool-cap trial, a multi-center randomized trial of therapeutic hypothermia for severe perinatal asphyxia, Selewski et.al(3) found that 38% of these newborns had AKI using a contemporary definition (the 2012 Kidney Disease Improving Global Outcomes (KDIGO)(4) definition). In this and other studies of perinatal asphyxia, the independent association between AKI and poor short and long-term clinical outcomes has been well documented. Furthermore, with our enhanced understanding of the pathophysiology and the epidemiology of AKI in other populations, experts no longer consider AKI simply a marker of the death process, but instead, an active contributor to this poor outcomes (5).

Despite our understanding of the impact of AKI on clinical outcomes, there are no FDA approved therapies to prevent or mitigate AKI. There have been several important challenges that have made it difficult to find such interventions. First, studies in adults are compromised by a multitude of underlying risk factors (such as smoking, diabetes, and pre-existing chronic kidney disease) which can confound results. Second, the etiology of AKI is sometimes multi-factorial. Third, the timing of the AKI (and the intervention) is late or unknown. In neonates with perinatal asphyxia, these important limitations are not present and thus, they constitute an ideal population to study the effects of interventions on the natural process of kidney damage.

During acute hypoxemia, adenosine levels increase as ATP hydrolysis exceeds synthesis resulting in intra-renal vasoconstriction, decreased renal perfusion, and drop of glomerular filtration rate (GFR). Four randomized controlled trials of severely asphyxiated neonates, three involving term and one involving preterm infants, found that a single prophylactic dose of theophylline, an adenosine receptor antagonist, administered within 1 hour of birth had a renoprotective effect (6–9). These studies consistently found that those randomized to intra-venous theophylline had lower serum creatinine (SCr) values and higher urine output on

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postnatal days 2 and beyond. Based on these studies, KDIGO AKI guidelines for the management of AKI suggest that single dose of theophylline should be considered in severely asphyxiated infants at high risk for AKI.(10)

In this month's *Acta Pediatric*, Raina et al. (11) provide additional evidence to support the use a single dose of theophylline as an adjunct to care in neonates with perinatal asphyxia. This study, entitled Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. represents the largest randomized placebo-controlled trial on theophylline for perinatal asphyxia to date. The investigators randomized 159 infants from their institutions in India between November 1, 2011 and October 31, 2012 with the following inclusion criteria: term gestation, birthweight > 2500 grams and birth asphyxia (2 or more of the following: Apgar ≤ 3 at 1 or ≤5 at 5 minutes, ≥ 10 minutes of positive pressure ventilation, seizure, severe hypotonia and a Thompson score > 15). Permuted block randomization yielded 78 infants that received 5 mg/kg IV theophylline and 81 received placebo. No infants received therapeutic hypothermia. There were no major difference between underlying baseline characteristics between groups. Those randomized to placebo had lower rates of AKI by KDIGO (15 vs. 49%) had lower SCr values on day 3 of life (0.83 ± 0.35 vs. 1.47± 0.61), and had less rates of oliguria (27% vs. 59%), less hematuria and less proteinuria. No complications from theophylline were reported. The investigators were unable to show a difference in survival between groups, although there was a trend for lower mortality in the theophylline group. They did not assess any long-term outcomes.

Should all neonates with perinatal asphyxia receive a single dose of theophylline? Perhaps, but there continues to be unresolved questions that should be answered in a systematic fashion before widespread practice. First, we need to understand the role of theophylline in context of the current standard of care, which includes the use of systemic hypothermia as this has been shown to significantly improve long-term survival/neurocognitive outcomes(12). Second, the main study outline for this study was a difference in SCr at postnatal day 3 of life. It is possible that is an excellent surrogate outcomes of hard clinical outcomes, such as mortality, length of stay, and long-term chronic kidney disease; however, there is insufficient data to determine this at this time. Ideally, hard clinical outcomes will be needed to fully elucidate if theophylline is efficacious to ameliorate / prevent the consequences of AKI. Further studies to determine surrogate outcomes in this population would be beneficial. Third, as the use of theophylline may have some potential harmful neurologic effects (13), adequately powered large multi-center studies will be needed to further evaluate these potential complications.

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References

1. Sarkar S, Barks JD, Bhagat I, Donn SM. Effects of therapeutic hypothermia on multiorgan dysfunction in asphyxiated newborns: whole-body cooling versus selective head cooling. J Perinatol. 2009; 29:558–563. [PubMed: 19322190]
2. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi DJ, et al. Neonatal Acute Kidney Injury. Pediatrics. 2015; 136:e463–e473. [PubMed: 26169430]
3. Selewski DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. J Pediatr. 2013; 162:725–729. e1. [PubMed: 23149172]
4. Fleming GM, Askenazi DJ, Bridges BC, Cooper DS, Paden ML, Selewski DT, et al. A multicenter international survey of renal supportive therapy during ECMO: the Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) group. ASAIO J. 2012; 58:407–414. [PubMed: 22588147]
5. Srisawat N, Kellum JA. Acute kidney injury: definition, epidemiology, and outcome. Curr Opin Crit Care. 2011; 17:548–555. [PubMed: 22027404]
6. Eslami Z, Shajari A, Kheirandish M, Heidary A. Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iran J Kidney Dis. 2009; 3:222–226. [PubMed: 19841526]
7. Cattarelli D, Spandrio M, Gasparoni A, Bottino R, Offer C, Chirico G. A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed. 2006; 91:F80–F84. [PubMed: 16204359]
8. Bakr AF. Prophylactic theophylline to prevent renal dysfunction in newborns exposed to perinatal asphyxia--a study in a developing country. Pediatr Nephrol. 2005; 20:1249–1252. [PubMed: 15947981]
9. Jenik AG, Ceriani Cernadas JM, Gorenstein A, Ramirez JA, Vain N, Armadans M, et al. A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. Pediatrics. 2000; 105:E45. [PubMed: 10742366]
10. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012:1–138.
11. Raina A, Pandita A, Harish R, Yachha M, Jamwal A. Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. Acta Paediatr. 2016 xx: xx-xx.
12. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013; 1:CD003311. [PubMed: 23440789]
13. Al-Wassia H, Alshaikh B, Sauve R. Prophylactic theophylline for the prevention of severe renal dysfunction in term and post-term neonates with perinatal asphyxia: a systematic review and meta-analysis of randomized controlled trials. J Perinatol. 2013; 33:271–277. [PubMed: 22836872]