# A Systematic Review and Meta-Analysis of Theophylline for Acute Kidney Injury in Asphyxiated Neonates

By

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A Master's Paper submitted to the faculty of
the University of North Carolina at Chapel Hill
in partial fulfillment of the requirements for
the degree of Master of Public Health in
the Public Health Leadership Program

Chapel Hill

Summer 2017

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## ABSTRACT

*Background*: Perinatal asphyxia is caused by decreased oxygen delivery to neonates during the birthing process, and leads to significant neonatal morbidity and mortality. Acute kidney injury due to decreased oxygen delivery is a major adverse neonatal health outcome associated with perinatal asphyxia, and can lead to renal failure. Previous studies in low resource settings lacking induced hypothermia (the current standard of care in well-resourced countries) have used theophylline administered immediately following asphyxiation to prevent (or reduce) kidney injury.

*Purpose:* To synthesize the current evidence on prophylactic theophylline in term infants with perinatal asphyxia for the prevention or treatment of acute kidney injury.

*Methods*: PubMed and EMBASE were searched from database inception through April 2016 using predefined criteria to identify RCTs comparing prophylactic theophylline to placebo in term infants following perinatal asphyxia examining incidence of acute kidney injury (AKI), serum creatinine levels (SCr), or glomerular filtration rates (GFR).

*Results*: Five RCTs met full inclusion criteria (N=356 infants) and were included in meta-analysis. The use of prophylactic theophylline was associated with a significant reduction in acute kidney injury compared with placebo (RR 0.36, 95% CI, 0.25 to 0.5; $p < 0.00001$). SCr levels were significantly lower in the theophylline group on days 3 and 5. Similarly, GFR levels were significantly increased on days 3 and 5 in the theophylline group compared to the control group.

*Conclusions*: Prophylactic theophylline administration significantly reduces the incidence of acute kidney injury in asphyxiated term neonates and should be considered for routine use in low-resource settings lacking access to therapeutic hypothermia. Future research should examine theophylline in conjunction with therapeutic hypothermia, optimal dosing, and safety.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AAP | American Academy of Pediatrics |
| aEEG | amplitude integrated electroencephalogram |
| AKI | acute kidney injury |
| AKIN | Acute Kidney Injury Network |
| BUN | blood urea nitrogen |
| CI | confidence interval |
| CNS | central nervous system |
| DALY | disability adjusted life-year |
| HIE | hypoxic ischemic encephalopathy |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| RCT | randomized control trial |
| RIFLE | Risk, Injury, Failure, Loss, and End-Stage Kidney Disease |
| RR | relative risk |
| SCr | serum creatinine |
| USPSTF | United States Preventive Services Task Force |

## INTRODUCTION

Perinatal asphyxia is a relatively common condition affecting newborns and can lead to significant morbidity and mortality. It is caused by reduced oxygenation due to decreased oxygen delivery during the birthing period. Perinatal asphyxia is a global problem, as an estimated 1.2 million deaths worldwide can be attributed to birth asphyxia.[1] As of 2006, the incidence of birth asphyxia was 4.3-8% in developed countries; however, the incidence was found to be much greater in developing countries at 23%.[2,3] Asphyxiation leads to serious adverse perinatal health outcomes; the most common is hypoxic ischemic encephalopathy (HIE), with an estimated incidence of 50-72%.[4] Birth asphyxia is the fifth most common cause of childhood death under 5 years worldwide[5] and also causes significant life-long morbidity, such as severe neurodevelopmental issues, cerebral palsy, and epilepsy. These disabilities are estimated to cause a 42 billion disability adjusted life year (DALY) burden on society.[5]

Perinatal asphyxia can be caused by placental abruption, vasa previa, uterine rupture, shoulder dystocia, cord prolapse, maternal cardiopulmonary arrest, and difficult or prolonged labor.[6] The lack of neonatal oxygen from complications surrounding labor can result in serious long-term neurological sequelae such as brain damage resulting in cerebral palsy, seizures, as well as mental and physical disability. HIE is a major complication that results from severe perinatal asphyxia. As the signs and symptoms of HIE can be non-specific and similar to those that occur during other forms of infantile encephalopathy, there is no formal definition for the diagnosis of HIE. However, one definition states that infants with HIE typically display low Apgar scores, low cord pH, neonatal seizures, and encephalopathy surrounding an asphyxiation event during labor and delivery.[7] Neonatal encephalopathy is defined as a “heterogenous, clinically defined syndrome caused by a disturbance in neurological function in an infant born at

or beyond 35 weeks of gestation, manifested by a decreased level of consciousness or seizures, and often with difficulty initiating and maintaining respirations, as well as depression of tone and reflexes".[7]

Asphyxiation triggers a protective reflex in which blood is re-routed to the heart, brain, and adrenals to preserve vital organ functioning representing the first stage of the injury. The second stage of injury occurs once the neonate has been delivered and stabilized. Approximately six hours following birth, biochemical cascades induce oxidative stress, inflammation, and cytotoxicity.[8] This second round of hypoxic-ischemic injury is thought to be the main driver of neurologic damage, so the current and only recommended treatment for reducing neurological outcomes related to HIE is induced hypothermia (also called therapeutic hypothermia) initiated within six hours of delivery.[9] Between 2005 and 2011, six randomized control trials (RCTs) were conducted examining induced hypothermia for neonatal encephalopathy.[10-15] Two out of the six studies used the induced hypothermia method of selective head cooling,[10,13] while the other four studies used the whole body cooling method.[11,12,14,15] Despite using the two different methods for cooling, all six studies included infants at least 35 weeks gestational age at birth cooled to a target temperature of 33.5-34.5ºC by at least 72 hours after birth followed by a slow rewarming period in which the temperature is only increased by 0.5ºC per hour. Based on these clinical trials, the American Academy of Pediatrics (AAP) recommends candidates for induced hypothermia meet the inclusion criteria of being $\geq$ 36 weeks of age and $\leq$ 6 hours of age and having an Apgar score $\leq$ 5 at 10 minutes after birth, or having a continued need for resuscitation at 10 minutes after birth, or having a pH < 7.0 or base deficit $\geq$ 16 mmol/L in umbilical cord blood or venous or arterial blood samples within an hour after birth, or having moderate to severe encephalopathy on clinical exam, or lastly having a moderately abnormal background for

20 minutes or seizure activity on an amplitude integrated electroencephalogram (aEEG) after one hour of age.[16] While whole-body cooling seems to be effective in reducing neurologic sequelae, there is little data on the effects of this treatment for other organ system damage. Despite the lack of specific treatment for other organ system injuries, damage to the heart, diaphragm, and kidneys frequently occurs.

The kidneys of neonates are particularly susceptible to damage during perinatal asphyxiation. At birth, the neonatal kidneys only receive 2.5 to 4.0% of the cardiac output compared to 20 to 25% of the cardiac output received by adult kidneys.[17] After birth, blood flow increases gradually over the next few weeks reaching almost to adult levels by 6 weeks. As the newborn kidneys are not receiving the complete amount of blood flow until around 6 weeks, they are highly susceptible to any changes in perfusion. The renin-angiotensin system along with prostaglandins also plays a role in helping the neonatal kidney adapt to life outside of the womb.[17] However, this system is also fragile and easily affected periods of stress such as those caused by perinatal asphyxia. During asphyxiation, blood flow to the kidneys is reduced, leading to renal hypoperfusion, acute kidney injury, and potentially renal failure.[6,18] HIE specifically accounts for 30-40% of acute kidney injury in the newborn period.[19,20] Mortality rates due to AKI from asphyxia is unknown. .[4]

Challenges in the field of neonatology often arise due to lack of evidence from controlled trials enrolling neonates. Much of the research on neonatal treatments for various medical conditions have been studied in children first and then scaled down to infants. Due to the paucity of published controlled trials in the literature, many existing protocols are based on expert opinion and recommendation.

A challenge in analyzing the amount of AKI and renal dysfunction due to perinatal asphyxia is that there are currently multiple different definitions for AKI used in the neonatal population. While in adults, there is a specific definition of AKI, there is no official internationally recognized definition for neonatal AKI, which has led to heterogeneity in the literature and in clinical practice. In 2008, AKI was frequently arbitrarily defined in studies as an absolute serum creatinine (SCr) ≥ 1.5 mg/dL.[17] Further studies such as the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) study and Acute Kidney Injury Network (AKIN) with their own definition of AKI.[21,22] Following these studies, a definition of AKI was created was created that merged the definitions from the RIFLE and AKIN studies called the Kidney Disease Improving Outcomes (KDIGO) guidelines, which are based on the absolute rise of SCr from a previous nadir and are recommended for use in children up to 120 days. According to the KDIGO guidelines, AKI is defined as having any of the following: increase in SCr by ≥ 0.3 mg/dL within 48 hours, or an increase in SCr to ≥ 1.5 times baseline (known or presumed to have occurred within the prior 7 days), or a urine volume < 0.5 ml/kg/h for 6 hours.[23] The KDIGO guidelines also give staging criteria based on the severity of AKI to further help guide treatment.[23] While the KDIGO guidelines offer a reasonable starting point for defining acute kidney injury, pediatric nephrologists and neonatologists at the 2013 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop concluded that more research needed to be done regarding the specific degree of SCr rise, age of use, and how to deal with a rise of 0.2 to 0.3 (which is technically a 1.5 –fold increase, therefore meeting AKI criteria).[17] The definitions of neonatal AKI that are most commonly used are a combination of rising SCr > 1.5 mg/dL with absolute cut-off values for the presence or absence of AKI, oliguria (1 ml/kg/h) and elevated blood urea nitrogen (BUN) > 39.9 mg/dL.[4]

The majority of AKI that occurs after HIE is pre-renal kidney injury.[20] As such, supportive measures such as intravenous fluids and blood pressure control are mainstays of treatment for kidney injury. While supportive treatments for AKI in the asphyxiated should be continued, additional interventions may prevent and improve outcomes associated with AKI in the asphyxiated neonate population. Some literature suggests that adenosine receptor antagonists, such as theophylline and aminophylline, may be effective in preventing and improving AKI associated with neonatal asphyxia. These medications are becoming more commonly used in low resource settings outside of the United States that do not have access to induced hypothermia.

Historically, theophylline has been implemented to successfully treat apnea of prematurity. In this setting, theophylline acts at a respiratory stimulant by acting on the respiratory center of the central nervous system to reduce apnea frequency and improve ventilation via their ability to cause dilation of pulmonary vasculature.[24] Theophylline has also been suggested to be beneficial for weaning premature infants from mechanical ventilation.[25,26] These drugs have been shown to stimulate the central nervous system (CNS) at all levels.[24] One commonly reported side effect of toxic doses of aminophylline is CNS excitation leading to restlessness and seizures.[27] The contraction, rate, and rhythm of the heart are also affected, and so can lead to tachycardia even at therapeutic doses.[24] Methylxanthines also cause dilatation of systemic vascular systems, but constriction of cerebral vasculature.[24] They cause stimulation of skeletal muscles, but relaxation of smooth muscles.[24] In the gastrointestinal tract, methylxanthines can cause stimulation of gastric acid and fluid secretion.[24] Lastly, methylxanthines cause increased renal blood flow and diuresis in the kidneys. In the kidneys, adenosine receptor antagonists such as theophylline and aminophylline function by blocking

renal adenosine, which acts as a vasoconstrictor metabolite after hypoxemia.[28] These adenosine receptor antagonists work independently from the inhibition of cyclic AMP phosphodiesterase.[29] Cytochrome P4501A2 is primarily responsible for the metabolism of theophylline in the adult kidney; however, this pathway is immature in the newborn kidney.[30] Therefore, understanding the proper dosing of methylxanthines in the newborn infant is especially important for maximizing the therapeutic benefits and reducing harms.

A few early studies in the 1980s examined the renal effects of different methylxanthines in newborn rabbits, whose renal maturation is highly similar to that of newborn infants.[31] These studies mainly used doses of methylxanthines (theophylline and aminophylline) that were commonly being used in the clinical setting for apnea of prematurity. One study comparing the effects of theophylline and caffeine demonstrated that the renal effects of methylxanthines were dose- and time-related after administration of 2.5 or 5 mg/kg theophylline.[32] In a follow-up study comparing theophylline to enprofylline, a xanthine derivative with low adenosine blocking properties, researchers found that a 5 to 10 fold lower concentration of theophylline showed the same profile of renal changes as the lower dose.[29] Specifically, these changes were an increase in filtration fraction and a slight increase in renal vascular resistance.[29] Theophylline was also found to increase diuresis and sodium excretion in newborn rabbits.[29]

Previous studies have also been performed to determine if prophylactic theophylline reduces kidney injury due to perinatal asphyxia. In 2012, a systematic review and meta-analysis was done to look specifically at 4 RCTs involving 197 infants total.[33] Compared to the placebo, prophylactic theophylline administration was associated with a significant reduction in severe renal dysfunction.[33] This research reflects the use of prophylactic theophylline to reduce acute kidney injury, but does not examine the use of theophylline for treating existing acute kidney

injury. In addition, this review does not include a newly published large RCT evaluating the efficacy of theophylline for preventing or improving renal dysfunction in term neonates with perinatal asphyxia.[28]

In summary, prophylactic treatment with methylxanthines like theophylline or aminophylline may be a promising strategy for reducing adverse renal dysfunction associated with perinatal asphyxia. The purpose of this review is to provide an up-to-date synthesis of the literature evaluating the efficacy of theophylline or aminophylline for preventing or treating AKI in term neonates with perinatal asphyxia.

## METHODS

*Questions*

The questions guiding our literature review were the following:

Q1: What is the efficacy of theophylline/aminophylline for reducing the incidence and severity of acute kidney injury in infants with perinatal asphyxia?

Q2: How does treatment affect measures of kidney function such as GFR, creatinine, and urinary β2 globulin?

Q3: What are the harms associated with the use of theophylline/aminophylline in infants with perinatal asphyxia?

*Search Strategy*

We searched PubMed and EMBASE from database inception through April 2017 for relevant published RCTs. The search strategies for PubMed and EMBASE are included in Appendix Table 1, and include relevant terms for the population, interventions, and outcomes of interest. Searches were limited to humans and English language, and search strategy was developed with the help of a health services librarian. First, the specific study population was retrieved using the search terms 'neonate', 'newborn', and 'infant'. To help specify the condition of interest, we searched for the terms 'asphyxiated', 'hypoxic ischemic encephalopathy', and 'HIE'. To investigate treatments, the terms 'theophylline' and 'aminophylline' were searched. Lastly, to look at the outcomes of interest, the search terms 'acute kidney failure' and more broadly using the search term "kidney". The Boolean search term 'and' was used to link the search terms.

*Study Selection Criteria*

All articles were independently searched for by the author and assessed for eligibility using predefined criteria (Table 1). Eligibility criteria were based on the PICOTSS format: (1) target population: term and post-term asphyxiated neonates, (2) interventions: adenosine antagonist (theophylline or aminophylline) for either prophylaxis or treatment, (3) comparison: placebo, (4) outcome: acute kidney injury as defined by use of measures of kidney function such as serum creatinine level, glomerular filtration rate, and urinary β2 microglobulin, and (5) study design: RCTs.

**Table 1: PICOTSS Search Criteria Used for Study Selection**

| | Include | Exclude |
|---|---|---|
| Language | English | Languages other than English |
| Populations | Term (Gestational age 37-40 weeks) neonates (0-28 days) with history of perinatal asphyxia<br>Examining prophylactic prescribing OR therapeutic prescribing for either theophylline/aminophylline | Preterm infants (<37 weeks gestational age)<br>Infants > 28 days<br>Neonates without a history of perinatal asphyxia<br>Neonates with other comorbid conditions |
| Setting | Neonatal intensive care units (NICU) | Studies not conducted in NICUs |
| Timing | Postnatal period | No exclusions for follow-up time |
| Treatment/ management interventions | Prophylactic theophylline/aminophylline for the prevention of AKI in HIE<br>Theophylline/aminophylline for treatment of AKI in HIE | All other interventions for preventing or reducing perinatal asphyxia |
| Comparisons | Prophylactic theophylline/aminophylline vs. no treatment for the prevention of AKI in HIE<br>Theophylline/aminophylline vs. no treatment for treating AKI in HIE | All other types of interventions for preventing or reducing perinatal asphyxia |
| Outcomes | Acute Kidney Injury (AKI)<br>Glomerular Filtration Rate (GFR)<br>B2-Microglobulin | Any other outcomes for measuring AKI<br>Any other biomarkers |
| Study designs | Randomized Control Trials (RCTs) | All other designs |

*Data Extraction*

Data extraction was performed by a single reviewer using a standardized data collection form. The following data were abstracted for all included studies: author, year, country, single-center or multi-center status, definitions adopted, overall sample size, group sample sizes, level of randomization, study setting, study duration, inclusion and exclusion criteria, duration of follow-up, demographic data, the proportion of patient with the primary outcome, and measured drug level if available. The primary outcome was the incidence of severe renal dysfunction. Secondary outcome measures were changes in serum creatinine, GFR, and urine β2-microglobulin, if available. Adverse reactions to treatment with theophylline or aminophylline were collected if they occurred within the first five days of life.

*Assessment of Trial Quality*

Assessment of randomized control trial quality was assessed by a single reviewer. The methodological quality of the individual studies was assessed using a single method. We assessed the quality of studies as good, fair, or poor, using pre-defined criteria developed by the United States Preventive Services Task Force (USPSTF) and adapted for this topic (Appendix A Table 2).[34]

*Data Synthesis and Analysis*

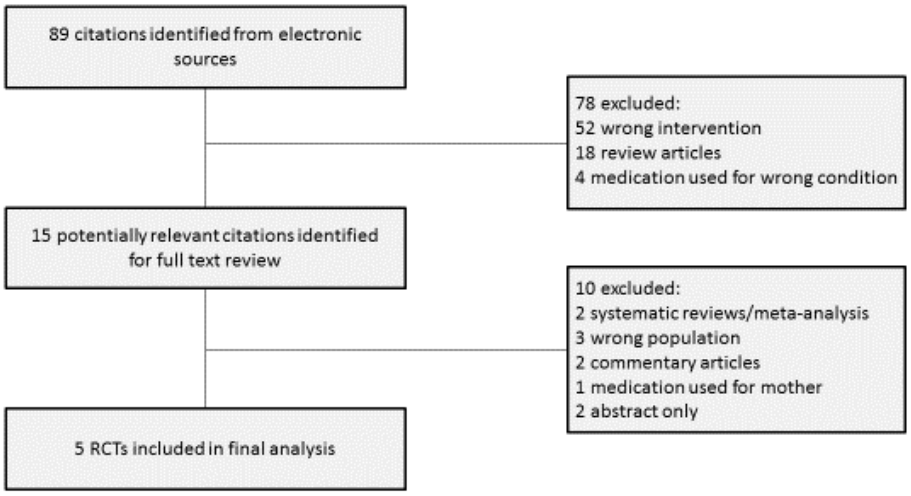
When multiple similar RCTs were available, quantitative synthesis was conducted with random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to estimate pooled effects. Review Manager (RevMan) Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) was used for all statistical analysis. To analyze categorical outcomes,

the risk ratios (RR) were estimated along with their 95% confidence intervals (CIs). Continuous outcomes were assessed using the weighted mean difference as well as the 95% CIs. For each outcome of interest, effect estimates were pooled assuming a random-effect modeling approach. Statistical heterogeneity across studies was assessed using both $I^2$ and Q statistics; $p< 0.05$ was defined to note statistical significance in the analysis of heterogeneity.

## RESULTS

The literature review results are shown in figure 1. In the initial database searches, 89 citations were identified; 78 were excluded as not relevant (primarily for wrong intervention, wrong study design or wrong population). The full-texts of 15 potentially relevant citations were reviewed and 5 RCTs met full eligibility criteria; full-text exclusion reasons are outlined in figure 1.

**Figure 1: Article Flow Diagram for Theophylline/Aminophylline Intervention**




*Study Characteristics*

Study characteristics are summarized in Table 2. All 5 included RCTs were conducted between 2000 and 2016, and all were conducted in non-US countries – Argentina, India, Egypt, and Iran.[28,35-38] Included studies used similar eligibility criteria for asphyxiation, such as a first minute Apgar Score less than or equal to 3 or a five minute Apgar score greater than or equal to 6, as well as the need for vigorous resuscitation using mask or endotracheal tube for positive

pressure ventilation. Four studies also used a base deficit of 15 mEq/L in cord blood or arterial blood gas.[36-38] Two mentioned the need for fetal distress.[36,37] Only one study mentioned the presence of seizures as an inclusion criteria for asphyxiation.[28] For defining acute kidney injury, all studies used a serum creatinine level of greater than or equal to 1.5 mg/dL for two consecutive days.[28,35-38] Three of the studies also used the criteria of a 0.3 mg/kg/day increase in serum creatinine.[36-38] All of the studies gave a single dose of IV theophylline to the intervention group within the first hour after birth[28,35-38]; however, three of the studies used a 5 mg/kg dose of theophylline[28,35,38] while the other two used an 8 mg/kg dose of theophylline.[36,37] Four out of five studies included a five day follow-up period[28,35,37,38], while one of the studies included a five day follow up period as well as followed up at one year.[36] All of the studies reported acute kidney injury as the primary outcome, while the secondary outcomes reported were serum creatinine (SCr), glomerular filtration rate (GFR), fluid balance, creatinine clearance, urinary sodium excretion, weight change, total urine output, and β2-microglobulin levels. Finally, only one study out of five reported theophylline levels during their study.[37]

## Table 2: Characteristics of Studies Included in Systematic Review and Meta-Analysis

| Study & Year | Country | Number of Infants | Inclusion Criteria for Asphyxia | Inclusion Criteria for AKI | THEO Dose | Timing of THEO Administration | Follow-up | Primary Outcomes Reported | Secondary Outcomes Reported | THEO Level Reported |
|---|---|---|---|---|---|---|---|---|---|---|
| Raina, 2016 | India | 159 | 1) Apgar < or = 3 in 1st minute or Apgar of up to 5 in the 5th minute 2) positive pressure ventilation for more than 10 minutes 3) seizures 4) severe hypotonia 5) Thomson score > 15 | Used Neonatal KDIGO Guidelines: a rise in SCr more than 1.5 times the lowest previous value | single dose of IV theophylline (5 mg/kg, 0.25 ml/kg) | Over a 5 minute period within the first hour of birth | 5 days | Acute Kidney Injury | Serum creatinine, GFR, fluid balance, creatinine clearance, urinary sodium excretion | No |
| Eslami, 2009 | Iran | 36 | 1) Apgar < or = 3 in 1st minute, or Apgar of < or = 6 in the 5th minute 2) base deficit higher than 15 mEq/L in cord or arterial blood sample 3) need for severe resuscitation | An increase in SCr ≥ 0.3 mg/dL or an SCr > 1.5 mg/dL for at least 2 consecutive days after a fluid challenge | slow single 5 mg/kg IV dose of theophylline | Within first 5 min after NICU admission, within 1 hour after birth | 5 days | Acute Kidney Injury | Serum and urinary creatinine, GFR, urinary sodium excretion | No |
| Baht, 2006 | India | 70 | 1) History of fetal distress 2) Need for immediate neonatal ventilation with a bag and mask or through endotracheal intubation for > 2 minutes after delivery 3) A 5-minute Apgar score of < or = 6 4) Base deficit ≥ 15 mEq/L in cord blood or admission arterial blood or cord blood pH <7 | SCr >1.50 mg/dl for two consecutive days and rising SCr level (0.3 mg/kg/day) | single dose of theophylline (8 mg/kg; 0.3 mL/kg) | Within the first hour after birth | 1 year | Acute Kidney Injury | Serum creatinine, urinary sodium excretion, fluid balance, weight changes, urine output | No |
| Bakr, 2005 | Egypt | 40 | 1) 5 min Apgar score of six or lower 2)base deficit >15 mEq/l in cord blood or admission blood gas 3) requirement of vigorous resuscitation (positive pressure ventilation and/or chest compression and/or use of adrenaline) | SCr >1.50 mg/dl for two consecutive days | single dose of 5 mg/kg IV theophylline, slow push over 5 minutes | Within the first hour after birth | 5 days | Acute Kidney Injury | Serum creatinine, fluid balance, creatinine clearance, GFR, β2-microglobulin | No |
| Jenik, 2000 | Argentina | 51 | 1) history of fetal distress (late decelerations decreased heart rate variability, or bradycardia (<100 bpm with or without meconium stained amniotic fluid) 2) 5-minute Apgar score of 6 or lower 3) base deficit equal to or greater than 15 mEq/L in cord blood or admission arterial blood sample 4) requirement of immediate neonatal ventilation with mask or tracheal tube for > 2 minutes after delivery | SCr > 1.50 mg/dL for at least 2 consecutive days after a fluid challenge consisting of a total of 20 mL/kg of normal saline, or rising levels of serum creatinine (0.3 mg/dL/day) | single dose of IV theophylline (8 mg/kg; 1.6 mg/kg) | Over a 5 minute period within the first hour after birth | 5 days | Acute Kidney Injury | Serum creatinine, fluid balance, creatinine clearance, GFR, urinary sodium excretion, urinary β2-microglobulin | Yes |

Note: To meet the criteria for asphyxiation, infants must meet at least two of the inclusion criteria. To meet the criteria for AKI, infants must meet the individual criteria listed above.

*Quality of Included Studies*

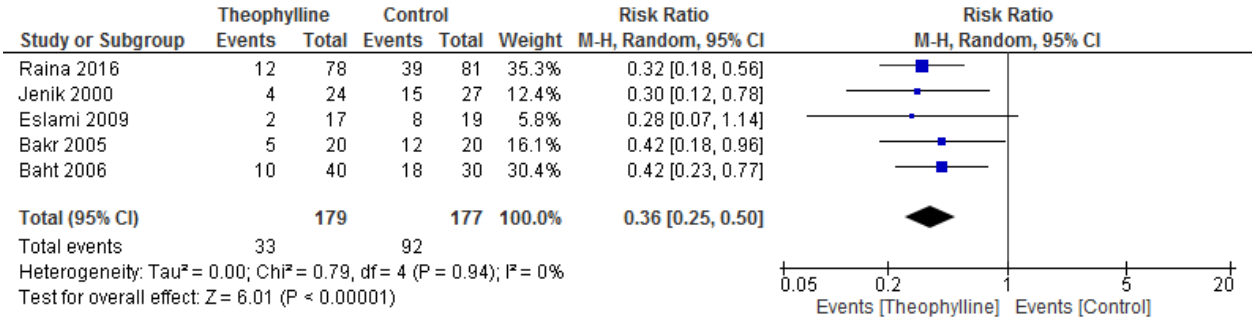
Quality assessment for all included RCTs is detailed in Appendix B Table 1. All studies were rated as good quality. One methodological flaw of the studies was small sample sizes; even the most recent study by Raina, et al., which included 159 infants, was underpowered as they were not able to recruit enough patients into the study. Selection bias and measurement bias risk was found to be low in all studies. Only the Jenik, et al. study was a multicenter trial, while the rest took place at single centers. The attrition rates were found to be low as all of the studies reported complete follow-up at five days with all of the infants included in the trial. However, only one study continued to follow the infants further, every two weeks after birth to two months and then monthly up to 1 year of age.[36] All studies used similar and appropriate strategies for statistical analysis. For a complete quality evaluation for each individual RCT included in the analysis, see Appendix B, Tables 2-6.

*Results*

*Incidence of Acute Kidney Injury*

Five randomized control trials were included in the meta-analysis. Data was used for a total of 356 infants, with 179 infants receiving treatment with theophylline and 177 receiving the control of either normal saline or a 5-10% dextrose solution. All trials included acute renal failure as their primary outcome and evidence of risk reduction (RR) for the use of theophylline in severely asphyxiated term infants. The overall pooled RR for developing acute kidney injury using a random-effects model was 0.36 (95% CI, 0.25 to 0.5; $p < 0.00001$) (Figure 2). There was no evidence of statistical heterogeneity between studies ($I^2 = 0\%$, $\chi 2 = 0.79$, $P = 0.94$).

**Figure 2: Forest plot of relative risks and 95% confidence intervals (CIs) for acute kidney injury in asphyxiated neonates who received theophylline as compared with placebo from five RCTs.**



*Differences in Serum Creatinine and Glomerular Filtration Rate*

All five studies included in the meta-analysis examined serum creatinine (SCr) levels and glomerular filtration rates for severely asphyxiated term infants treated with either theophylline or the control. Table 3 shows a summary of the data reported in each study over five days. For the analysis, data from days 1, 3, and 5 were included as these values for SCr and GFR were given in all five studies.

Figure 3 shows a forest plot of the differences in SCr levels and 95% CIs between the theophylline and control groups from the five RCTs. For SCr on day 1, there was evidence of high statistical heterogeneity across studies ($I^2$=90%, $\chi^2$=41.97, $p < 0.0001$). Moderate heterogeneity on day 3 was found to be not statistically significant ($I^2$=37%, $\chi^2$=6.38, p=0.17). On day 5, high statistical heterogeneity was found across studies for differences in SCr levels ($I^2$=75%, $\chi^2$= 15.92, p=0.003). Using a random effects model, the pooled estimate of SCr on day 1 was found to be not statistically significant at -0.19 (95% CI, -0.44 to 0.07; p=0.16). However, SCr on days 3 and 5 favored the theophylline group and was statistically significant. On day 3, the pooled estimate of SCr was -0.56 (95% CI, -0.72 to -0.40; p<0.0001). On day 5, the pooled estimate of SCr was -0.35 (95% CI, -0.53 to -0.16; p=0.002).

Figure 4 shows a forest plot of the differences in GFR levels and 95% CIs between the theophylline and control groups from the five RCTs. For GFR, the tests for heterogeneity were not significant across studies on day 1 ($I^2$=47%, $\chi^2$=5.65, p=0.13), day 3 (I2=0%, $\chi$2=0.09, p=0.99), and day 5 ($I^2$=47%, $\chi^2$=5.63, p=0.13). Using a random effects model, the pooled estimate of GFR on day 1 was found to be not statistically significant at 1.17 (95% CI, -2.82, 5.16; p=0.56). However, statistically significant improvements in GFR were found on days 3 and 5. For day 3, the pooled estimate of GFR was found to be 14.30 (95% CI, 11.73 to 16.87;

$p<0.00001$). On day 5, the pooled estimate of GFR was estimated to be 10.5 (95% CI, 5.81 to 14.29; $p<0.00001$).

*Secondary Results Reported by Included Trials*

For our analysis, we did not include non-clinically significant outcomes such as fluid balance, creatinine clearance, urinary sodium excretion, weight change, total urine output, and β2-microglobulin levels. Urinary creatinine levels and urinary sodium levels are not a reliable measure for acute kidney injury. Similarly, fluid balance, weight gain, and total urine output are subjective measures that could be affected by clinical practice and as such were not included in the analysis. Statistical tests were performed for β2-microglobulin examining heterogeneity between studies and pooled estimates of the differences between treatment with theophylline and the control. However, there were only two studies that included data for β2-microglobulin. A forest plot of the results are located in the appendix.

**Table 3: Serum Creatinine and Glomerular Filtration Rate as Reported in the RCTs in the study.**

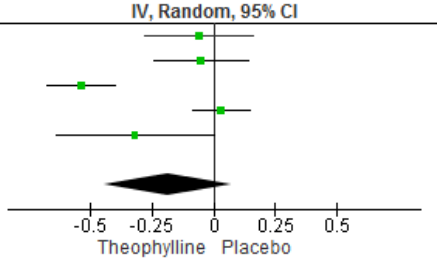
| Study & Year | Outcome Measure | Day 1 | | Day 2 | | Day 3 | | Day 4 | | Day 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | THEO | Control | THEO | Control | THEO | Control | THEO | Control | THEO | Control |
| Raina, 2016 | Serum creatinine (mg/dL) | 1.22 ± 0.68 | 1.28 ± 0.51 | N/A | N/A | 0.83 ± 0.35 | 1.47 ± 0.61 | N/A | N/A | 0.82 ± 0.52 | 1.09 ± 0.63 |
| Eslami, 2009 | | 0.92 ± 0.22 | 0.86 ± 0.20 | N/A | N/A | 0.63 ± 0.22 | 1.06 ± 0.47 | N/A | N/A | 0.56 ± 0.14 | 0.73 ± 0.14 |
| Baht, 2006 | | 1.18 ± 0.69 | 1.5 ± 0.68 | 0.92 ± 0.65 | 1.56 ± 0.92 | 0.95 ±0.50 | 1.59 ± 0.92 | 0.94 ± 0.45 | 1.62 ± 1.03 | 0.82 ± 0.47 | 1.57 ± 0.90 |
| Bakr, 2005 | | 1.23 ± 0.19 | 1.20 ± 0.19 | 1.22 ± 0.24 | 1.41 ± 0.29 | 1.24 ± 0.39 | 1.57 ± 0.61 | 1.31 ± 0.38 | 1.59 ± 0.44 | 1.29 ± 0.27 | 1.47 ± 0.41 |
| Jenik, 2000 | | 1.0 ± 0.3 | 1.05 ± 0.4 | 0.97 ± 0.17 | 1.51 ± 0.41 | 1.02 ± 0.69 | 1.94 ± 1.1 | 0.89 ± 0.7 | 1.59 ± 0.7 | 0.71 ± 0.2 | 1.36 ± 0.9 |
| | | | | | | | | | | | |
| Raina, 2016 | GFR (ml/min) | 28.21 ± 22.27 | 21.37 ± 13.55 | N/A | N/A | 32.16 ± 16.34 | 17.73 ± 7.92 | N/A | N/A | 41.47 ± 27.24 | 32.7 ± 26.67 |
| Eslami, 2009 | | 25.4 ± 7.3 | 28.2 ± 12.8 | N/A | N/A | 42.4 ± 19.1 | 27.5 ± 10.7 | N/A | N/A | 42.3 ± 12.5 | 37.5 ± 6.5 |
| Baht, 2006 | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Bakr, 2005 | | 21.10 ± 9.3 | 22.11 ± 8.7 | 25.13 ± 9.1 | 15.32 ± 7.1 | 26.02 ± 10.8 | 12.39 ± 4.6 | 27.48 ± 10.2 | 14.35 ± 6.8 | 29.31 ± 9.9 | 19.10 ± 8.7 |
| Jenik, 2000 | | 23.17 ± 10.3 | 22.07 ± 9 | 24.01 ± 8.6 | 14.9 ± 6.8 | 25.94 ±11.2 | 11.36 ± 5.1 | 27.29 ± 9.1 | 32.41 ± 7.4 | 32.41 ± 7.4 | 18.0 ± 9.8 |

**Figure 3: Forest plot of relative risks and 95% confidence intervals (CIs) of differences in serum creatinine levels between theophylline and control groups from five RCTs on day 1, day 3, and day 5.**

**Day 1:**

| Study or Subgroup | Theophylline Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Raina 2016 | 1.22 | 0.68 | 78 | 1.28 | 0.74 | 81 | 19.6% | -0.06 [-0.28, 0.16] |
| Jenik 2000 | 1 | 0.3 | 24 | 1.05 | 0.4 | 27 | 20.3% | -0.05 [-0.24, 0.14] |
| Eslami 2009 | 0.32 | 0.22 | 17 | 0.86 | 0.2 | 19 | 21.5% | -0.54 [-0.68, -0.40] |
| Bakr 2005 | 1.23 | 0.19 | 20 | 1.2 | 0.19 | 20 | 21.8% | 0.03 [-0.09, 0.15] |
| Baht 2006 | 1.18 | 0.69 | 40 | 1.5 | 0.68 | 30 | 16.8% | -0.32 [-0.64, 0.00] |
| **Total (95% CI)** | | | **179** | | | **177** | **100.0%** | **-0.19 [-0.44, 0.07]** |

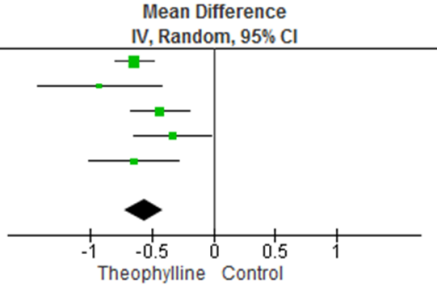
Heterogeneity: Tau² = 0.08; Chi² = 41.97, df = 4 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.41 (P = 0.16)




**Day 3:**

| Study or Subgroup | Theophylline Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Raina 2016 | 0.83 | 0.35 | 78 | 1.47 | 0.61 | 81 | 36.2% | -0.64 [-0.79, -0.49] |
| Jenik 2000 | 1.02 | 0.69 | 24 | 1.94 | 1.1 | 27 | 8.4% | -0.92 [-1.42, -0.42] |
| Eslami 2009 | 0.63 | 0.22 | 17 | 1.06 | 0.47 | 19 | 24.6% | -0.43 [-0.67, -0.19] |
| Bakr 2005 | 1.24 | 0.39 | 20 | 1.57 | 0.61 | 20 | 16.9% | -0.33 [-0.65, -0.01] |
| Baht 2006 | 0.95 | 0.5 | 40 | 1.59 | 0.92 | 30 | 13.9% | -0.64 [-1.00, -0.28] |
| **Total (95% CI)** | | | **179** | | | **177** | **100.0%** | **-0.56 [-0.72, -0.40]** |

Heterogeneity: Tau² = 0.01; Chi² = 6.38, df = 4 (P = 0.17); I² = 37%
Test for overall effect: Z = 6.99 (P < 0.00001)




**Day 5:**

| Study or Subgroup | Theophylline Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Raina 2016 | 0.82 | 0.52 | 78 | 1.09 | 0.63 | 81 | 23.1% | -0.27 [-0.45, -0.09] |
| Jenik 2000 | 0.71 | 0.2 | 24 | 1.36 | 0.9 | 27 | 14.3% | -0.65 [-1.00, -0.30] |
| Eslami 2009 | 0.56 | 0.14 | 17 | 0.73 | 0.14 | 19 | 27.5% | -0.17 [-0.26, -0.08] |
| Bakr 2005 | 1.29 | 0.27 | 20 | 1.47 | 0.41 | 20 | 21.0% | -0.18 [-0.40, 0.04] |
| Baht 2006 | 0.82 | 0.47 | 40 | 1.57 | 0.9 | 30 | 14.1% | -0.75 [-1.10, -0.40] |
| **Total (95% CI)** | | | **179** | | | **177** | **100.0%** | **-0.35 [-0.53, -0.16]** |

Heterogeneity: Tau² = 0.03; Chi² = 15.92, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 3.69 (P = 0.0002)

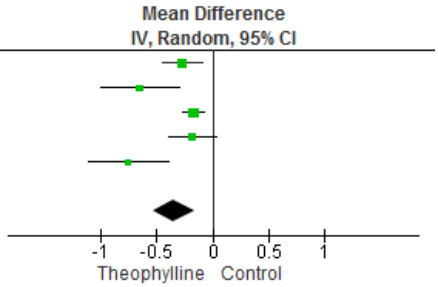
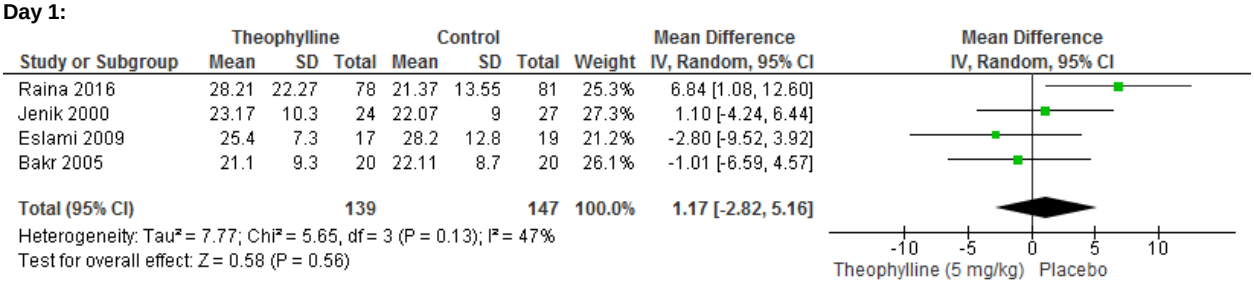
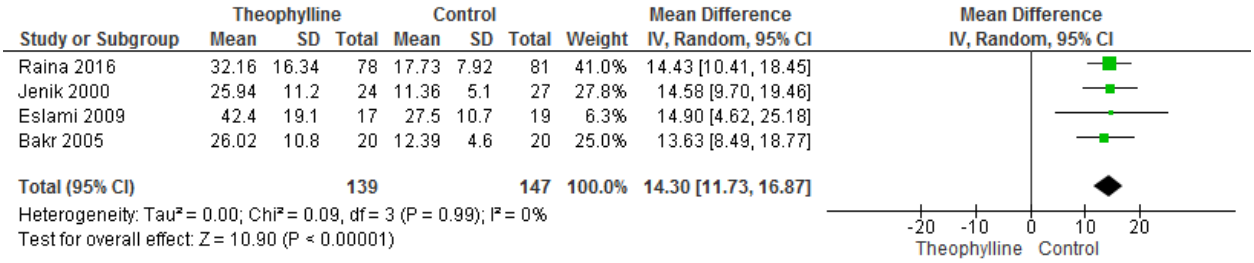


**Figure 4: Forest plot of relative risks and 95% confidence intervals (CIs) of differences in glomerular filtration levels between theophylline and control groups from five RCTs on day 1, day 3, and day 5.**

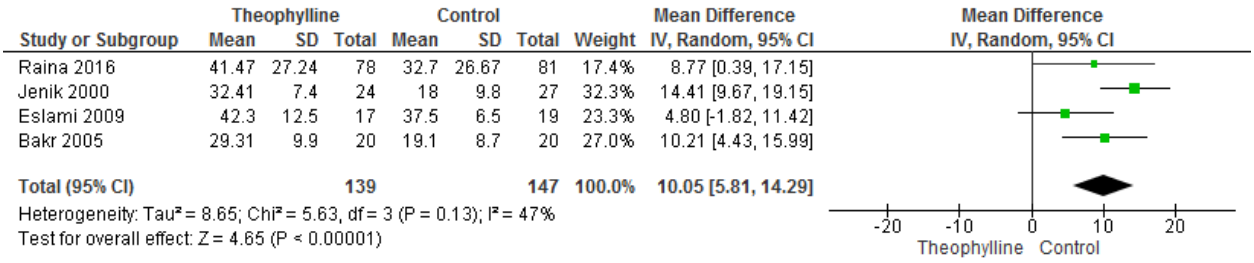
**Day 1:**




**Day 3:**




**Day 5:**



## DISCUSSION

The goal of this systematic review and meta-analysis was to determine whether theophylline could prevent or ameliorate acute kidney injury in term neonates with perinatal asphyxia. Ultimately five RCTs were included in the review and meta-analysis. Our results indicate that prophylactic theophylline given within the first hour after birth is associated with a reduction in the incidence of acute kidney injury compared with placebo (RR 0.36 (95% CI, 0.25 to 0.5; $p < 0.00001$)). We also found that markers of renal injury such as serum creatinine and glomerular filtration rates also improved with the administration of theophylline.

Although results for reduction in incidence of AKI were consistent across trials, there were some differences across studies in the magnitude of effect. For example, dosing of theophylline was one issue that may have affected the results of the meta-analysis. Three of the five included studies used a 5 mg/dL single IV dose based on previous studies of apnea of prematurity[28,35,38], while two of the studies used a single 8 mg/dL IV dose[36,37] based on a different study of apnea of prematurity.[39] While our results show a low $I^2$ indicating that the amount of heterogeneity between studies was low, the magnitude of effect for the change in creatinine appeared to be greater in the two studies that used the 8 mg/kg theophylline dose compared with the 5 mg/kg dose suggesting that the higher dose may confer more therapeutic benefits. Currently, there are no studies that have directly compared different dosing of theophylline in neonates for acute kidney injury in infants with perinatal asphyxiation. Future studies must be conducted to address the optimal dosing of theophylline in these patients as well as what numerical difference in these biological markers indicates actual observable clinical benefits to these patients.

In the literature on prophylactic theophylline for prevention or reduction of acute kidney

injury in asphyxiated term neonates, very little is reported about the toxicity and possible harms of theophylline. In all of the past studies, only a single dose of theophylline was given depending on the specific study (either 5 mg/kg or 8 mg/kg), thus limiting any direct comparisons that could be made about its toxicity. While treatment with theophylline confers such benefits as a reduction of acute kidney injury, commonly associated harms of theophylline include seizures and CNS excitability.[24] Notably, theophylline has a narrow therapeutic index making the optimal selection of the dose critical.[30] In the five RCTs used in the study, harms are mentioned such as death from the causes of multi-organ failure, persistent pulmonary hypertension of the newborn secondary to meconium aspiration, and severe encephalopathy. Other harms reported in the study were seizures, cerebral hemorrhage, hematuria, proteinuria, and requirement of a blood transfusion. While all five studies quantified the incidence of different types of harms during their studies, no RCTs directly attributed any harms to theophylline use. It cannot be concluded that these harms are a result of theophylline treatment as no analysis was performed to reduce confounding factors. Perinatal asphyxiation is a serious and complicated condition. Variation with individual clinical regimens as well as center to center variation in treatment of asphyxiation and its common comorbidities may be affecting the negative outcomes observed by the studies.

All five studies were completed in nations outside of the US – one in Argentina, one in Egypt, one in Iran, and two in India. Researchers from these countries were interested in finding an effective treatment for ameliorating acute kidney injury in asphyxiated neonates as they do not have the resources for hypothermic cooling. Induced whole-body infant cooling (also called induced hypothermia) is the mainstay of treatment for HIE in developed countries. This method is thought to work by eliminating the second round of hypoxic-ischemic damage to the brain that

occurs approximately six hours after an asphyxiation event. In 2013, a Cochrane review was conducted to determine the effect of therapeutic hypothermia with standard care on mortality, long-term neurodevelopmental outcomes, and side effect profile.[40] Their study was based on 11 randomized control trials and included 1505 term infants with moderate to severe encephalopathy. After analysis, the investigators found that therapeutic hypothermia resulted in statistically significant and clinically important reduction in mortality or major neurodevelopmental disability at 18 months of age, but had some adverse side effects of sinus bradycardia and thrombocytopenia.[40] However, little attention has been focused on whether or not induced hypothermia for HIE also improves outcomes related to AKI. Notably, none of the five RCTs used in our systematic review and meta-analysis directly compared theophylline versus hypothermic cooling for preventing or reducing acute kidney injury in this population. Also, none of these studies concurrently looked at the use of a prophylactic dose of theophylline with hypothermic cooling to examine whether using the treatments together could have additive beneficial effects. Future research both directly comparing theophylline and hypothermic cooling as well as research examining use of theophylline and hypothermic cooling is warranted.

*Strengths and Limitations*

Of the body of literature that exists on the use of prophylactic theophylline for acute kidney injury in asphyxiated neonates, this systematic review and meta-analysis is the most comprehensive to date. While there were only five RCTs included in the analysis, a strength of this review is that our analysis included analysis of the SCr level of 356 infants and the GFR of 286 infants, which are the largest numbers to be included in a meta-analysis of this nature. Also, due to lack of data, we could not conduct a subgroup analysis to examine factors that could be

affected heterogeneity between the studies. In terms of methods, this review used a comprehensive literature search and quality assessment of all included trials; one limitation (due to time and resources) was that a single reviewer conducted the literature review and data abstraction.

*Clinical Implications*

This review and meta-analysis provides evidence that the prophylactic use of theophylline significantly decreases the incidence of acute kidney injury and causes significant improvement in other secondary measures of renal injury such as SCr and GFR over a five day period in term asphyxiated neonates. As these studies were limited to the narrow study population severely asphyxiated neonates $\geq$ 37 weeks, the efficacy of theophylline for the prevention of acute kidney injury in younger, older, or less sick populations cannot be determined at this time. While promising for potential use in future clinical practice, further studies should assess the optimal dose of theophylline to incur maximum benefits and minimal harms. Although some harms were mentioned in the study, small sample sizes and the lack of further analysis to investigate possible confounders of these harms need to be more closely evaluated.

## CONCLUSIONS

The goal of this systematic review and meta-analysis was to determine whether theophylline could prevent or ameliorate acute kidney injury in term neonates with perinatal asphyxia. These results indicate that prophylactic theophylline given within the first hour after birth is associated with a reduction in the incidence of acute kidney injury. We also found that markers of renal injury such as serum creatinine and glomerular filtration rates also improved with the administration of theophylline. This study provides the largest amount of evidence to date in favor of using prophylactic theophylline to prevent acute kidney injury in neonates with perinatal asphyxia. The conclusions of this review are especially important as the use of theophylline may drastically improve renal outcomes in low resource countries without access to induced hypothermia, the current standard of care for perinatal asphyxiation in well-resourced countries. As there have been no studies directly comparing treatment with theophylline to induced hypothermia for acute kidney injury in asphyxiated neonates, more research must be done in the future to see if theophylline could be used alone or concomitantly with induced hypothermia to improve acute kidney injury in well-resourced NICUs. Lastly, more studies must be done to examine the optimal dosing of theophylline treatment in the neonatal population as well as potential adverse effects.

## APPENDIX A: Methods

### Appendix A Table 1. PubMed and EMBASE Search Strategy

| Database | PubMed |
|---|---|
| **Search Strategy** | #1 AND #2 AND #3 AND #4 |
| #1 | ("theophylline"[MeSH Terms] OR "theophylline"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields]) AND ("kidney"[MeSH Terms] OR "kidney"[All Fields]) |
| #2 | ("theophylline"[MeSH Terms] OR "theophylline"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields]) AND ("kidney"[MeSH Terms] OR "kidney"[All Fields]) |
| #3 | ("theophylline"[MeSH Terms] OR "theophylline"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields]) AND ("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields]) |
| #4 | HIE[All Fields] AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields]) AND ("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields]) |
| | |
| **Database** | **EMBASE** |
| **Search Strategy** | #1 AND #2 AND #3 AND #4 |
| #1 | theophylline AND infant AND kidney |
| #2 | (theophylline/exp OR theophylline) AND (infant/exp OR infant) AND acute AND (kidney/exp OR kidney) AND (injury/exp OR injury) |
| #3 | theophylline AND newborn AND acute AND kidney AND failure |
| #4 | hie AND infant AND acute AND kidney AND injury |

## Appendix A Table 2. RCT Quality Appraisal Tool

| Critical Appraisal of Health Literature | |
|---|---|
| Citation (JAMA style) | |
| Study Question and Research Design | |
| Source Population | |
| Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc.) | |
| Initial Comparability of Groups (ie randomization or group composition; concealment of allocation) | |
| Drop-outs (no endpoint data), adherence, crossovers (attrition, loss to follow-up) | |
| Potential for Selection Bias (High, Medium, or Low) and Explain | |
| Measurement of exposure, intervention, potential counfounders, and outcomes; reliability and validity of measurement, how performed, blinding | |
| Potential for Measurement Bias (High, Medium, or Low) | |
| Potential Confounders (name and describe how each was controlled for) | |
| Potential for Confounding (High, Medium, or Low) | |
| Analysis (Intention to treat or other adjustment) | |
| Results: magnitude and direction (point estimate); random error or precision (confidence interval); statistical significance | |
| Clinical and Public Health importance for the source population; for a wider population | |
| Overall judgement of internal validity (good, fair, or poor) | |
| External Validity: applicability to other populations | |
| Comments and Overall Conclusions/Interpretations (include consistency with other studies; biological plausibility; conflicts of interest; selective endpoint reporting | |

## APPENDIX B: Results

## APPENDIX B Table 1. Summary of the Methodological Quality of Included RCTs

| Study | Single or Multicenter | Randomization Process Described | Allocation Concealment | Blinding | Placebo-Controlled | Complete Follow-up | Overall Quality Rating |
|---|---|---|---|---|---|---|---|
| Raina, 2016 | Single Center | Yes | Not described | Yes | Yes | Yes | Good |
| Eslami, 2009 | Single Center | No | Not described | Yes | Yes | Yes | Good |
| Baht, 2006 | Single center | No | Not described | Yes | Yes | Yes | Good |
| Bakr, 2005 | Single center | No | Not described | Yes | Yes | Yes | Good |
| Jenik, 2000 | Multicenter | Yes | Yes | Yes | Yes | Yes | Good |

## APPENDIX B Table 2. Critical Appraisal of Raina, 2016

| Critical Appraisal of Health Literature | |
|---|---|
| Citation (JAMA style) | Raina, A. et al. Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. *Acta Paediatrica*. 2016; 105. 448-51. |
| Study Question and Research Design | Does theophylline prevent or ameliorate renal dysfunction in term neonates with perinatal asphyxia?<br>Randomized Control Trial |
| Source Population | Tertiary care clinic in India from Nov. 1, 2011 to October 31, 2012 |
| Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc.) | • All infants recruited were born in obstetric unit of the study center or referred from local hospitals<br>• Term gestation (≥ 37 weeks)<br>• >2500 grams<br>• With severe birth asphyxia |
| Initial Comparability of Groups (ie randomization or group composition; concealment of allocation) | Groups comparable; permuted block randomization performed by person not related to study<br>159 included in the study<br>78 neonates in theophylline group<br>81 neonates in control group |
| Drop-outs (no endpoint data), adherence, crossovers (attrition, loss to follow-up) | No dropouts, adherence issues, or cross-over |
| Potential for Selection Bias (High, Medium, or Low) and Explain | Low potential for selection bias |
| Measurement of exposure, intervention, potential counfounders, and outcomes; reliability and validity of measurement, how performed, blinding | Intervention: single dose of IV theophylline (5 mg/kg)<br>Control: single dose of IV normal saline (0.25 mg/kg)<br>Both given over 5 minute period within first hour of birth<br>Both provided in syringes with same external appearance (blinding)<br>Used Apgar scores , Sarnat & Sarnat system, and Thomson score to grade asphyxia<br>Used neonatal KDIGO guidelines to determine severe renal dysfunction<br>Measured 24 hr fluid intake, urine output, SCr, Cr clearance, UCr, Na+ excretion, GFR at 1, 3, 5 days<br>Also measured incidence of death. |
| Potential for Measurement Bias (High, Medium, or Low) | Low measurement bias |
| Potential Confounders (name and describe how each was controlled for) | Many measurements used in study could be affected by clinical practice or are not meaningful in terms of understanding kidney function.<br>Asphyxiated children very sick, so this could affect results, especially causes of death. Of the causes of death reported in the study, many of these may not have been directly related to theophylline administration. No analysis was performed to further evaluate causes of death. |
| Potential for Confounding (High, Medium, or Low) | Medium potential for confounding |
| Analysis (Intention to treat or other adjustment) | No intention to treat analysis performed; based on previous studies, assumed incidence of AKI was 40% in control group and 20% in theophylline group. A sample size of 164 was found to give a power of 85 and confidence interval of 95%. However, they were only able to recruit 159 patients. |
| Results: magnitude and direction (point estimate); random error or precision (confidence interval); statistical significance | • AKI present in 12 (15%) in theophylline group & 39 (48%) of control group ($p<0.01$)<br>• 33 deaths (21%) deaths in study cohort: 15 in theophylline group (6 from multi-organ failure, 6 from PPHTN of newborn secondary to meconium aspiration, & 3 from severe encephalopathy); 18 deaths in the placebo group (12 from multi-organ failure, 3 from severe encephalopathy, and 3 from PPHTN)<br>• No significant difference in 24-hr fluid balance<br>• Mean urine output significantly greater in theophylline group with only 21 (27%) developing oliguria compared to 48 (59%) in the placebo group. |
| Clinical and Public Health importance for the source population; for a wider population | Theophylline appears to be a promising way for low resource countries to improve kidney injuries caused by asphyxia. In countries with greater resources, standard of care for HIE is hypothermic cooling. Additional large multicenter trials with long term-follow up periods are needed to help compare theophylline treatment to hypothermic cooling. |
| Overall judgement of internal validity (good, fair, or poor) | Fair; because they were unable to recruit the number of infants required to power their study |
| External Validity: applicability to other populations | Very specific population that results can be applied to (term neonates, >2500 grams, with severe perinatal asphyxiation); however, perinatal asphyxiation is relatively common so treatment could have widespread use within the perinatology-neonatology community. |
| Comments and Overall Conclusions/Interpretations (include consistency with other studies; biological plausibility; conflicts of interest; selective endpoint reporting | Overall, a single dose of theophylline may be helpful in improving or eliminating acute kidney injury in asphyxiated newborns. This may be especially helpful in low resource areas where they are not able to perform hypothermic cooling. These results are consistent with other studies looking at theophylline and is the largest study to date. They were unable to recruit enough infants to give their study the statistical power they wanted; however, they were only missing a small amount of subjects and their results are consistent with past literature. Biological plausible study. No conflicts of interest or selective endpoint reporting. |

## APPENDIX B Table 3. Critical Appraisal of Eslami, 2009

| Critical Appraisal of Health Literature | |
|---|---|
| Citation (JAMA style) | Eslami, Z. et al. Theophylline for Prevention of Kidney Dysfunction in Neonates with Severe Asphyxia. *Iranian J of Kidney Diseases*. 2009; 3:4; 222-226. |
| Study Question and Research Design | Can theophylline prevent or ameliorate kidney dysfunction in term neonates with perinatal asphyxia?<br>Randomized Control Trial |
| Source Population | NICU of Shahid Sadoughi Hospital, Yazd, Iran between January 2007 to April 2008 |
| Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc.) | • All infants were admitted within their first 5 days of life to the NICU<br>• Term gestation (≥37 weeks)<br>• ≥2500 grams<br>• With severe birth asphyxiation |
| Initial Comparability of Groups (ie randomization or group composition; concealment of allocation) | Groups comparable; randomly assigned infants into groups based on a random number table<br>41 infants included in the study<br>17 infants in theophylline group<br>19 infants in control group |
| Drop-outs (no endpoint data), adherence, crossovers (attrition, loss to follow-up) | No dropout, adherence issues, or cross-over |
| Potential for Selection Bias (High, Medium, or Low) and Explain | Low potential for selection bias |
| Measurement of exposure, intervention, potential counfounders, and outcomes; reliability and validity of measurement, how performed, blinding | Intervention: single dose of IV theophylline (5 mg/kg)<br>Control: single dose of 10% dextrose solution (2 mg/kg)<br>Both given in the first 5 minutes after NICU admission during the first hour after birth<br>No mention of blinding<br>Used Apgar scoring to select patients<br>AKI defined as an increase in SCr level ≥ 0.3 mg/dL or SCr level higher than 1.5 mg/dL for at least 2 consecutive days<br>Measured 24 hour fluid intake, urinary volume, Ucr, SCr, serum electrolytes (Na, K, & Ca), and urinary Na excretion on the 1st, 3rd, and 5th days. Also measured hematuria.<br>Noted incidence of acute kidney injury as well as other complications related to asphyxiation |
| Potential for Measurement Bias (High, Medium, or Low) | Medium; due to lack of blinding of those who are administering treatment & control |
| Potential Confounders (name and describe how each was controlled for) | Many measurements used in study could be affected by clinical practice or are not meaningful in terms of understanding kidney function.<br>Asphyxiated children very sick, so this could affect results, especially causes of death. Researchers did indicate that complications were determined to be due to asphyxiation. |
| Potential for Confounding (High, Medium, or Low) | Medium potential for confounding |
| Analysis (Intention to treat or other adjustment) | No intention to treat analysis. Performed chi-square test, Fisher exact test, and t test for comparisons between groups. |
| Results: magnitude and direction (point estimate); random error or precision (confidence interval); statistical significance | AKI was detected in 2 of the theophylline infants (11.8%) and 8 of the control infants (42.1%) during the first 5 days after birth (p=0.04)<br>The estimated GFRs were not significantly different on days 1 and 5, but were significant on day 3 (p=0.02).<br>SCr was not significantly different on day 1. On day 3, the levels significantly decreased in the theophylline group and increased in the controls (p<0.001). On day 5, SCr decreased in both groups.<br>Sodium excretion was significantly higher in the theophylline group than the control group on day 1 (p=0.02).<br>Two patients died from multi-organ failure and PPHTN. |
| Clinical and Public Health importance for the source population; for a wider population | Prophylactic theophylline given early after birth has beneficial effects in reducing acute kidney injury in neonatal asphyxia. May be promising in low resource areas. |
| Overall judgement of internal validity (good, fair, or poor) | Fair; they did not report any blinding in their study; small sample size |
| External Validity: applicability to other populations | Very specific population that results can be applied to (term neonates, >2500 grams, with severe perinatal asphyxiation); however, perinatal asphyxiation is relatively common so treatment could have widespread use within the perinatology-neonatology community. |
| Comments and Overall Conclusions/Interpretations (include consistency with other studies; biological plausibility; conflicts of interest; selective endpoint reporting | Overall, a single dose of theophylline may be helpful in improving or eliminating acute kidney injury in asphyxiated newborns. This may be especially helpful in low resource areas where they are not able to perform hypothermic cooling. Problems with this study were the low sample size and the lack of blinding. However, these results are consistent with other studies looking at theophylline and acute kidney injury. Biological plausible study. No conflicts of interest or selective endpoint reporting. |

## APPENDIX B Table 4. Critical Appraisal of Baht, 2006

| Critical Appraisal of Health Literature | |
|---|---|
| Citation (JAMA style) | Baht, MA; et al. Theophylline for renal function in term neonates with perinatal asphyxia: A randomized, placebo-controlled trial. *J Pediatr*. 2006; 149: 180-4. |
| Study Question and Research Design | Can prophylactic theophylline reduce the incidence and/or severity of renal failure in term infants with perinatal asphyxia?<br>Randomized Control Trial |
| Source Population | Infants were recruited from NICU of the Sheri Kashmir Institute of Medical Sciences (SKIMS) in Soura, Srinagar, India over 36 month period from January 2001 to December 2003 |
| Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc.) | • All infants included were born in the obstetric department of SKIMS, Lalded Women's Hospital, and 2 maternity homes located near SKIMS<br>• Term gestation (≥ 37 weeks)<br>• Severe perinatal asphyxia |
| Initial Comparability of Groups (ie randomization or group composition; concealment of allocation) | Groups comparable; randomized treatment groups; allocation was concealed<br>70 infants were included in the study<br>40 infants were in the theophylline group<br>30 infants were in the treatment group |
| Drop-outs (no endpoint data), adherence, crossovers (attrition, loss to follow-up) | No dropouts, adherence issues, or cross-overs |
| Potential for Selection Bias (High, Medium, or Low) and Explain | Low potential for selection bias |
| Measurement of exposure, intervention, potential counfounders, and outcomes; reliability and validity of measurement, how performed, blinding | Intervention: single IV dose of theophylline (8 mg/kg)<br>Control: single IV dose of 5% dextrose in water (of equal volume)<br>Both given within an hour of birth<br>Investigators & caregivers were blinded to the assignment of the patients<br>Used Apgar scoring to select patients<br>AKI defined as SCr > 1.5 mg/dL for 2 consecutive days and rising SCr level of 0.3 mg/kg/day<br>Measured SCr, 24 hr fluid intake and urine volume in first 5 days of life, daily inputs/outputs, urinary Na and creatinine measures, GFR, β2-microglobulin<br>Noted deaths, AKI, as well as other complications |
| Potential for Measurement Bias (High, Medium, or Low) | Low potential for measurement bias |
| Potential Confounders (name and describe how each was controlled for) | Many measurements used in study could be affected by clinical practice or are not meaningful in terms of understanding kidney function.<br>Asphyxiated children very sick, so this could affect results, especially causes of death. Of the causes of death reported in the study, many of these may not have been directly related to theophylline administration. No analysis was performed to further evaluate causes of death. |
| Potential for Confounding (High, Medium, or Low) | Medium potential for confounding |
| Analysis (Intention to treat or other adjustment) | No intention to treat analysis; performed student t-test, 2-way analysis of variance with repeated measure of a single factor |
| Results: magnitude and direction (point estimate); random error or precision (confidence interval); statistical significance | The incidence of AKI was similar in both groups on the day of birth, but was increased in the control group on days 2-5 of life.<br>The excretion of β2-microglobulin was lower in the theophylline group. (6.7±2.4 mg/L vs. 15.2±5.6 mg/L; p=<0.001)<br>In infants with AKI, serum creatinine and creatinine clearance returned to normal within 1 month, while the β2-microglobuline levels returned to normal within 6 weeks.<br>Of the 6 infants that died during the study, 4 infants (10%) were in the theophylline group while 2 infants (6%) were in the control group. This difference was found to be not statistically significant (p >0.1)<br>Also, include statement in abstract about the GFR being lower in the control than in the theophylline treatment group, but data is not reported elsewhere in the paper. |
| Clinical and Public Health importance for the source population; for a wider population | Prophylactic theophylline given early after birth has beneficial effects in reducing acute kidney injury in neonatal asphyxia. May be promising in low resource areas. |
| Overall judgement of internal validity (good, fair, or poor) | Fair; small sample sizes included in the study |
| External Validity: applicability to other populations | Very specific population that results can be applied to (term neonates, >2500 grams, with severe perinatal asphyxiation); however, perinatal asphyxiation is relatively common so treatment could have widespread use within the perinatology-neonatology community. |
| Comments and Overall Conclusions/Interpretations (include consistency with other studies; biological plausibility; conflicts of interest; selective endpoint reporting | Overall, a single dose of theophylline may be helpful in improving or eliminating acute kidney injury in asphyxiated newborns. This may be especially helpful in low resource areas where they are not able to perform hypothermic cooling. A problem with this study was the low sample size and failure to fully account for the deaths and other complications that may or may not be due to theophylline treatment. Also, claim that there is a difference in GFR in their abstract, but results are not actually shown anywhere in the paper. Positives of the study were that they used blinding, they followed infants with AKI every 2 weeks during the first 2 months of life and then monthly up to 1 year, as well as the inclusion of another renal biomarker called β2-microglobulin. These results are also consistent with other studies looking at theophylline and acute kidney injury. Biological plausible study. No conflicts of interest or selective endpoint reporting. |

## APPENDIX B Table 5. Critical Appraisal of Bakr, 2005

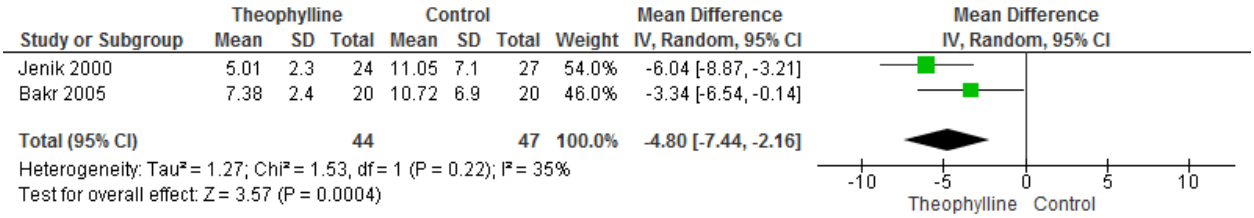
| Critical Appraisal of Health Literature | |
|---|---|
| Citation (JAMA style) | Bakr, AF. Prophylactic theophylline to prevent renal dysfunction in newborns exposed to perinatal asphyxia–a study in a developing country. *Pediatr Nephrol*. 2005; 20: 1249-1252. |
| Study Question and Research Design | Can theophylline prevent and/or ameliorate renal dysfunction in term neonates with perinatal asphyxia?<br>Randomized Control Trial |
| Source Population | Newborn unit of Alexandria University Children's Hospital, Alexandria, Egypt |
| Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc.) | • Term gestation or post-term gestation (≥37 weeks)<br>• With severe birth asphyxiation |
| Initial Comparability of Groups (ie randomization or group composition; concealment of allocation) | Groups comparable at baseline; enrolled newborns were randomized to two treatment groups; investigator was blinded to group assignments; same unit protocol for asphyxiation management was applied to both groups<br>40 infants included in the study<br>20 infants in the theophylline group<br>20 infants in the control group |
| Drop-outs (no endpoint data), adherence, crossovers (attrition, loss to follow-up) | No drop-outs, adherence issues, or cross-overs |
| Potential for Selection Bias (High, Medium, or Low) and Explain | Low potential for selection bias |
| Measurement of exposure, intervention, potential counfounders, and outcomes; reliability and validity of measurement, how performed, blinding | Intervention: single IV dose of theophylline (0.5 mg/kg)<br>Control: single IV 2 cc D10W<br>Both given within the first hour of birth<br>Investigators were blinded to group assignments; no mention of caretaker blinding<br>Used Apgar scoring to select patients<br>Measured SCr, GFR, serum electrolytes, urine creatinine, β2-macroglobulin, and hematuria daily during 1st five days of life<br>Also measured 24 hour fluid intake, urine volumes, and weight during the 1st five days of life<br>Lastly, measured patient deaths, causes, and complications |
| Potential for Measurement Bias (High, Medium, or Low) | Low potential for measurement bias |
| Potential Confounders (name and describe how each was controlled for) | Many measurements are not especially useful as they could be affected by clinical practice or are not meaningful in terms of understanding kidney function.<br>Asphyxiated children are very ill, so this could affect results, especially causes of death and complications. Of the causes of death reported in the study, many of these may not have been directly related to theophylline administration. No analysis was performed to further evaluate causes of death. |
| Potential for Confounding (High, Medium, or Low) | Medium potential for confounding |
| Analysis (Intention to treat or other adjustment) | No intention to treat analysis mentioned; results were analyzed by Student's t and chi$^2$ tests. |
| Results: magnitude and direction (point estimate); random error or precision (confidence interval); statistical significance | AKI was present in 5 (25%) of the theophylline group and in 12 (60%) of the control group ($X^2$=2.9, p<0.05)<br>SCr values were similar between the two groups on day 1, but were significantly different the second day onwards (p<0.05 on day 2, day 3, day 4, and day 5)<br>GFR was significantly decreased in the placebo group after day 1 (p<0.05 on day 2, day 3, day 4, and day 5)<br>β2-microglobulin excretion was significantly less in the theophylline group on all days (p<0.05)<br>Two deaths were reported: 1 in theophylline group (PPHTN) and 1 in control group (sepsis) |
| Clinical and Public Health importance for the source population; for a wider population | Prophylactic theophylline given early after birth has beneficial effects in reducing acute kidney injury in neonatal asphyxia. May be promising in low resource areas. |
| Overall judgement of internal validity (good, fair, or poor) | Fair; small sample sizes in study; reported data for all 5 days rather than 1, 3, and 5; did not blind the caretakers |
| External Validity: applicability to other populations | Very specific population that results can be applied to (term or post-term neonates with severe perinatal asphyxiation); however, perinatal asphyxiation is relatively common so treatment could have widespread use within the perinatology-neonatology community. |
| Comments and Overall Conclusions/Interpretations (include consistency with other studies; biological plausibility; conflicts of interest; selective endpoint reporting | Overall, prophylactic theophylline treatment given shortly after birth has beneficial effects for the reduction of AKI in asphyxiated full-term infants, with no significant changes in CNS involvement. This treatment may be especially helpful in low resource areas where they are not able to perform hypothermic cooling. A problem with this study was the low sample size and failure to fully account for the deaths and other complications that may or may not be due to theophylline treatment. Positives of the study were that they used blinding as well as the inclusion of another renal biomarker called β2-microglobulin. These results are also consistent with other studies looking at theophylline and acute kidney injury. Biological plausible study. No conflicts of interest or selective endpoint reporting. |

# APPENDIX B Table 6. Critical Appraisal of Jenik, 2000

| Critical Appraisal of Health Literature | |
|---|---|
| Citation (JAMA style) | Jenik, AG. 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. |
| Study Question and Research Design | Can theophylline prevent and/or ameliorate renal dysfunction in term neonates with perinatal asphyxia?<br>Randomized Control Trial |
| Source Population | Infants born at 3 hospitals of Buenos Aires, Argentina (Hospital Italiano, Sanatorio Guemes, and Clinica Maternal Lomas) |
| Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc.) | • Term gestation or post-term gestation (≥37 weeks)<br>• With severe birth asphyxia |
| Initial Comparability of Groups (ie randomization or group composition; concealment of allocation) | Groups comparable at baseline; infants randomized by sequential computer-generated numbers; investigators and caregivers were blinded to treatment assignment; preparation of treatment and control was prepared by Pheonix Pharmaceutical (Buenos Aires, Argentina) with same external appearance and placed in consecutive numbered sealed opaque envelopes based on a randomized table with predetermined group allocation<br>51 infants were included in study<br>24 infants were in the theophylline group<br>27 infants were in the placebo group |
| Drop-outs (no endpoint data), adherence, crossovers (attrition, loss to follow-up) | No drop-outs, adherence issues, or crossovers |
| Potential for Selection Bias (High, Medium, or Low) and Explain | Low potential for selection bias |
| Measurement of exposure, intervention, potential counfounders, and outcomes; reliability and validity of measurement, how performed, blinding | Intervention: single IV dose of theophylline (8 mg/kg)<br>Control: single IV dose of 5% dextrose in water<br>Both were administered over a 5 minute period within the first hour after birth<br>Used Apgar scoring to select patients as well as the Score of Portman to determine the severity of the asphyxia<br>Measured 24 hour fluid intake and urine volumes during first 5 days of life<br>Daily SCr, electrolytes, and hematuria measured<br>GFR estimated on days 2 and 3<br>β2-microglobulin was measured on first voided urine 12 hours after theophylline administration<br>Recorded serum theophylline levels at 36 to 48 hours of life<br>Noted deaths and causes of death |
| Potential for Measurement Bias (High, Medium, or Low) | Low potential for measurement bias |
| Potential Confounders (name and describe how each was controlled for) | Many measurements are not especially useful as they could be affected by clinical practice or are not meaningful in terms of understanding kidney function.<br>Asphyxiated children are very ill, so this could affect results, especially causes of death and complications. Of the causes of death reported in the study, many of these may not have been directly related to theophylline administration. |
| Potential for Confounding (High, Medium, or Low) | Medium potential for confounding |
| Analysis (Intention to treat or other adjustment) | No intention to treat analysis was performed; Student's t-test was used to analyze continuous variables; Chi2 test was used for analysis of discrete data. |
| Results: magnitude and direction (point estimate); random error or precision (confidence interval); statistical significance | Theophylline treatment resulted in significant decrease in SCr (except for day 1, significant difference was found between groups, p<0.001) and urinary β2-macroglobulin (5.01±2.3 mg/L vs. 11.5 ±7.1 mg/L; p=0.005), with a significant increase in the creatinine clearance.<br>Serum theophylline levels were recorded at 36-48 hours of life with an average of 12.7 µg/mL (range: 7.5-18.9 µg/mL) versus trace levels (0.87 µg/mL) in control group.<br>GFR was markedly decreased in the placebo group as compared to the theophylline group (except for day 1, significant difference was found between groups, p<0.001)<br>4 deaths total during the study – 1 in theophylline group (PPHTN) and 3 in control group (2 due to multisystem organ failure & 1 due to sepsis) |
| Clinical and Public Health importance for the source population; for a wider population | Prophylactic theophylline given early after birth has beneficial effects in reducing acute kidney injury in neonatal asphyxia. May be promising in low resource areas. |
| Overall judgement of internal validity (good, fair, or poor) | Fair; sample sizes in the study were small and study should be completed in larger number of infants. This study also reported theophylline levels in the serum at 36-48 hours of life, that the other studies did not report. |
| External Validity: applicability to other populations | Very specific population that results can be applied to (term or post-term neonates with severe perinatal asphyxiation); however, perinatal asphyxiation is relatively common so treatment could have widespread use within the perinatology-neonatology community. |
| Comments and Overall Conclusions/Interpretations (include consistency with other studies; biological plausibility; conflicts of interest; selective endpoint reporting | Overall, treatment with a single 8 mg/kg dose of theophylline within the first postnatal hour in term neonates with severe asphyxia has beneficial effects reducing acute kidney injury. This treatment may be especially helpful in low resource areas where they are not able to perform hypothermic cooling, the current standard of care in well-resourced NICUs. A problem with this study was the low sample size. Positives of the study were that they used blinding as well as the inclusion of another renal biomarker called β2-macroglobulin, although they only looked at this at 12 hours post-theophylline administration. This study also reported theophylline levels in the serum at 36-48 hours of life, that the other later studies did not report. Biological plausible study. No conflicts of interest or selective endpoint reporting. |

**APPENDIX B: Figure 1 – Forest plot of differences in urinary β2-microglobulin levels and 95% confidence intervals (CIs) between theophylline and control groups on Day 1.**

**Day 1:**




Although there were only two studies, we were interested in examining the differences in urinary β2-microglobulin levels and 95% confidence intervals (CIs) between theophylline and control groups. Unfortunately due to lack of data, we were only able to analyze differences in the β2-microglobulin levels on day 1 across the two studies. The heterogeneity across studies was not statistically significant ($I^2$=35%, $\chi^2$=1.53, p=0.22). Using a random effects model, the pooled estimate of β2-microglobulin levels on day 1 was found to be -4.80 (95% CI, -7.44 to -2.16; p=0.0004) favoring asphyxiated infants treated with theophylline. Due to the small number of studies and study participants, further research needs to be performed focused on urinary β2-microglobulin levels.

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