Theophylline and aminophylline for prevention of acute kidney injury in neonates and children: a systematic review

Girish Chandra Bhatt,1 Priya Gogia,1 Martin Bitzan,2 Rashmi Ranjan Das3

ABSTRACT
Objective To compare the efficacy and safety of theophylline or aminophylline for prevention of acute kidney injury (AKI) in neonates and children.
Design Systematic review and meta-analysis with application of Grading of Recommendations, Assessment, Development and Evaluation system.
Data sources PubMed/MEDLINE, Embase, Google Scholar and Cochrane renal group were searched from 1970 to May 2018.
Eligibility criteria Randomised clinical trials and quasi-randomised trials comparing the efficacy and safety of prophylactic theophylline or aminophylline for prevention of AKI in neonates and children were included. The primary outcomes were: incidence of AKI, serum creatinine levels and all-cause mortality.
Results A total of nine trials were included in the qualitative synthesis. Six trials including 436 term neonates with birth asphyxia who received a single dose of theophylline were finally included in the meta-analysis. The pooled estimate showed 60% reduction in the incidence of AKI in neonates with severe birth asphyxia (RR: 0.40; 95% CI 0.3 to 0.54; heterogeneity: I²=0%) (moderate quality evidence), decrease in serum creatinine over days 2–5 (very low to low quality evidence) without significant difference in all-cause mortality (RR: 0.88; 95% CI 0.52 to 1.50; heterogeneity: I²=0%) (very low-quality evidence). A significant difference in the negative fluid balance, increase in GFR and decrease in urinary β2 microglobulin was seen in favour of theophylline.
Conclusion and relevance A single dose of prophylactic theophylline helps in prevention of AKI/severe renal dysfunction in term neonates with severe birth asphyxia (moderate quality evidence) without increasing the risk of complications and without affecting all-cause mortality (very low-quality evidence).
Trial registration number CRD 42017073600.

INTRODUCTION
Acute kidney injury (AKI) is defined as a rapid loss in kidney function (hours to days), resulting in derangements in fluid balance, electrolytes and waste products.1 AKI may result from impaired renal perfusion, exposure to nephrotoxic drugs, sepsis or ischaemia during surgery, such as cardio-pulmonary bypass.2 In a recent prospective national cohort study using electronic alert system, the incidence of hospital and community acquired AKI in children was found to be 40.1% and 29.4%, respectively.3 The reported incidence of neonatal AKI ranges from 8.4% to 34.5%4–5 and is associated with increased mortality, longer duration of hospital stay and an increased cost.6 7 A systematic review of large cohort studies conducted between 2004 to 2012 showed a pooled incidence of AKI in 33.7% children and a pooled mortality rate of 13.8%.8 Despite increased mortality, there are few modalities for prevention and treatment of AKI.

Some of the previous studies and randomised controlled trials (RCTs) have shown renoprotective role of theophylline and aminophylline in term9–13 and preterm neonates with severe birth asphyxia,14 children undergoing cardiac surgery15–16 and in preterm neonates with respiratory distress syndrome.17 A previous systematic review had shown improved outcome with use of a single dose of theophylline.18 Since then, two RCTs have been published.9 19 The previous review focused mainly on neonates with severe birth asphyxia; the description of outcome data was limited, and treatment emergent complications were excluded from the final meta-analysis. Thus, we conducted this updated systematic review including RCTs and quasi-randomised trials to explore the present evidence for the use of adenosine antagonists for prevention of AKI. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)20 approach to rate quality of evidence for primary outcomes and present our results with GRADE summary tables, which was also lacking in the previous systematic review.

What is already known on this topic?
► Acute kidney injury (AKI) is associated with increased mortality, longer duration of hospital stay and an increased cost.
► Care for neonates and children with AKI remains supportive.

What this study adds?
► A single dose of adenosine antagonists reduces the incidence of AKI in term neonates with severe birth asphyxia by 60% without increasing the risk of complications (moderate quality evidence).
► Prophylactic theophylline given to neonates with severe birth asphyxia also decreases serum creatinine, maintains negative fluid balance and increases glomerular filtration rate.
OBJECTIVE
To describe the efficacy and safety of theophylline or aminophylline compared with standard therapy or placebo for prevention of AKI in neonates and children.

METHOD
We included RCTs and quasi-RCTs (trials where allocation is not truly random, eg, by alternation, use of alternate medical record numbers, date of birth or other methods with a potential for selection bias).

Types of participants
Neonates and children (0–18 years) who received theophylline or aminophylline for prevention of AKI and compared with standard therapy or placebo were eligible. Exclusion criterion were: children with pre-existing renal disease, history of tachyarrhythmias, seizures, cardiac transplant recipients, small for gestational age, neonates requiring mechanical ventilation or history of drug intake by mother causing fetal and neonatal depression, children/infants requiring renal replacement therapy, deranged liver enzymes (>3 times normal) and coagulopathy.

The definition of AKI was taken as used in the individual study (table 1).

Search methods for identification of studies
Cochrane Central Register of Controlled Trials, PubMed/MEDLINE, Embase, Google Scholar and Cochrane renal group were searched from 1970 to May 2018. The following search strategy was applied: ((((((adenosine receptor antagonist OR adenosine antagonist) OR theophylline) OR aminophylline) OR caffeine)) AND (((((acute kidney injury) OR acute renal failure) OR acute Kidney Failure) OR renal failure) OR acute renal insufficiency) OR renal insufficiency) OR renal dysfunction) OR acute renal injury)) AND (((((Neonates) OR Newborn Infant) OR infant) OR preschool) OR toddler) OR paediatric) OR children). The paediatric age group includes patients up to 18 years.

Types of outcome measures
The primary and secondary outcomes were defined before the collection of data. The outcome measures were collected daily up to 5 or 7 days as specified in individual trials.

Primary outcome measures
1. Incidence of AKI/severe renal dysfunction in initial 7-day period.
2. Serum creatinine (mg/DL) levels daily up to 5 days.
3. All-cause mortality.

Secondary outcome measures
1. Fluid balance daily up to 5 days.
2. Estimated glomerular filtration rate (eGFR; mL/min/1.73 m²) daily up to 5 days.
3. Urinary β2 globulin levels (mg/L) during initial 5 days.
4. Disease complications and treatment emergent adverse events.

Treatment emergent adverse events have been defined as adverse events that have first occurred or worsened in severity after initiation of treatment.34

Data extraction (selection and coding)
Data were collected using a pilot tested data extraction form. Two authors (GCB and PG) independently extracted data including author, type of population, exposure/intervention (theophylline or aminophylline vs standard therapy or placebo), results (outcome measures, effect and significance) and sources of funding/support. Any disagreement in the extracted data was resolved by discussion with the third author (MB).

Risk of bias (quality) assessment
Two review authors (GCB and RRD) independently assessed the quality of the included trials by using Cochrane methodological quality assessment forms.32

Strategy for data synthesis
The data were pooled and expressed as mean difference (MD) with 95% CI for continuous data and risk ratio (RR) with 95% CI for categorical data. A p value <0.05 was considered significant. I² statistics was used for assessment of heterogeneity. In case of high-level heterogeneity (>50%), we tried to explore the cause. A fixed effect model was initially conducted and if significant statistical heterogeneity existed between trials (I² >50%), potential sources of heterogeneity were considered and where appropriate a random effects model was used. RevMan (Review Manager) V.5.2 was used for all the analyses.33

Publication bias
For publication bias, we used inverted funnel plot as suggested by Egger et al.24

Grade of evidence
For assessment of the quality of evidence we used GRADE Profiler software (V.3.2).25 GRADE assessment of evidence quality reflects confidence in the estimates of benefits or harms. GRADE is implemented with four levels of evidence quality, namely, high, moderate, low and very low. Rating is made for each outcome based on study design, risk of bias, imprecision, indirectness and magnitude of effect.26 ‘Summary of findings (SOF)’ tables were constructed by using GRADE profiler, and only primary outcomes were included in SOF tables.

Sensitivity analysis
We evaluated the impact of methodological quality by removing the trials at high or unclear risk of bias for random sequence generation and allocation concealment.

RESULTS
A total of 88 citations were retrieved by using the search strategy; after duplicate removal, 84 articles were available for screening of which 73 were excluded (title and/or abstract not relevant). The full texts of the remaining 11 articles were assessed for eligibility (figure 1). After further exclusion of two articles (one has evaluated the role of aminophylline in patients with chronic kidney disease (CKD), one has experimental drug in both the arms), nine trials were finally included in the qualitative synthesis (table 1). Six trials,9–13 19 with 436 participants, evaluated the effect of prophylactic theophylline for the prevention of severe renal dysfunction in term neonates with severe birth asphyxia. One trial17 evaluated the role of theophylline in preterm neonates <32 weeks’ gestation with respiratory distress syndrome, two trials evaluated the role of aminophylline—one in preterm neonates with birth asphyxia14 and another in infants and children undergoing cardiac surgery with cardiopulmonary bypass.15 Only two trials have low risk of bias in all the
<table>
<thead>
<tr>
<th>Study author</th>
<th>Setting, country</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes measured</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jenik et al</strong>&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Three centres, Argentina</td>
<td>Numbers (n=51): theophylline group (n=24); placebo group (n=27). Age: neonates. Inclusion criteria: neonates (term and post-term) with severe birth asphyxia defined as: history of fetal distress, 5 min Apgar score of 6 or lower and requirement of immediate neonatal ventilation. Exclusion criteria: condition not related to asphyxia, small for gestational age, congenital abnormalities of kidney or urinary tract, cardiovascular pathology not related to perinatal asphyxia, exposure to medications modifying haemodynamics and renal function, polycythaemia, clinical evidence of potential antenatal injury and pharmacological depression.</td>
<td>Theophylline group received single dose of 8 mg/kg over 5 min by infusion within first hour of birth. Placebo group received 5% dextrose in water.</td>
<td>1. Severe renal dysfunction. 2. Serum creatinine. 3. Fluid balance. 4. GFR. 5. Urinary sodium excretion. 6. Urinary β2 microglobulin. Severe renal dysfunction was defined by following criteria: serum creatinine &gt;1.5 mg/dL for at least two consecutive days or rising levels of serum creatinine (0.3 mg/dL) per day.</td>
<td>Blinding of outcome assessor not clear. Theophylline levels were not done.</td>
</tr>
<tr>
<td><strong>Bakr</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Single-centre NICU, Egypt</td>
<td>Numbers (n=40): theophylline group (n=20); placebo group (n=20). Age: term and post-term newborns. Inclusion criteria: newborns with severe birth asphyxia defined by: 5 min Apgar score of 6 or lower, base deficit &gt;15 mEq/L in cord or admission blood gas, requirement of vigorous resuscitation. Exclusion criteria: preterm and small for gestational age and neonates with congenital abnormality and dysmorphism.</td>
<td>Theophylline group received single dose of 5 mg/kg theophylline intravenously over 5 min. Placebo group received 2 mL of 10% dextrose.</td>
<td>1. Severe renal dysfunction. 2. Serum creatinine. 3. Fluid balance. 4. Creatinine clearance. 5. GFR. 6. Urinary β2 microglobulin and haematuria. Severe renal dysfunction was defined as: serum creatinine of &gt;1.5 mg/dL for two consecutive days.</td>
<td>Random sequence generation, allocation concealment and binding of outcome assessor not clear. Theophylline levels not done.</td>
</tr>
<tr>
<td><strong>Bhat et al</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Single centre NICU, India</td>
<td>Numbers (n=70): theophylline group (n=40); placebo group (n=30). Age: term and post-term neonates. Inclusion criteria: neonates with severe perinatal asphyxia defined by: history of fetal distress, need for immediate ventilation and a 5 min Apgar score of ≤5, base deficit &gt;15 mEq/L in cord blood or admission or cord blood pH &lt;7. Exclusion criteria: drugs used by mother that can affect renal haemodynamics and renal function, any condition unrelated to asphyxia, cardiovascular disease unrelated to asphyxia, congenital malformation of the kidneys or urinary tract, polycythaemia, microcephaly and chromosomal disorders or severe intrauterine growth disorders.</td>
<td>Theophylline group received 8 mg/kg intravenous theophylline over 5 min. Placebo group received equal amount of 5% dextrose in water.</td>
<td>1. Severe renal dysfunction. 2. Serum creatinine. 3. Urinary sodium excretion. 4. Fluid balance. 5. Weight change. 6. Urine output. Severe renal dysfunction was defined as: serum creatinine &gt;1.5 mg/dL for two consecutive days and rising serum creatinine level (0.3 mg/kg/day).</td>
<td>Random sequence generation, allocation concealment and binding of outcome assessor not clear. Theophylline levels not done.</td>
</tr>
<tr>
<td><strong>Cattarelli et al</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Single centre, Italy</td>
<td>Numbers (n=50): theophylline group (n=25); placebo group (n=25). Age: preterm neonates. Inclusion criteria: preterm neonates &lt;32 weeks gestation who developed respiratory distress syndrome within 6 hours and needed mechanical ventilation or nasal continuous positive pressure ventilation. Exclusion criteria: kidney or urinary tract congenital anomalies, congenital heart defects, prenatatal exposure to inhibitors of ACE or non-steroidal anti-inflammatory drugs and chromosomal disorders or multiple malformations.</td>
<td>Experimental group was given intravenous theophylline 1 mg/kg for 3 days. Control group was given equal volume of placebo, that is, 5% dextrose in water for 3 days.</td>
<td>1. Urine output. 2. Serum creatinine. 3. GFR. 4. Serum electrolytes. 5. Urinary β2 microglobulin. 6. Complications.</td>
<td>The trial has low risk of bias in all domains. Theophylline levels were measured.</td>
</tr>
<tr>
<td><strong>Eslami et al</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Single centre, Iran</td>
<td>Numbers (n=36): theophylline group (n=18); placebo group (n=18). Age: neonates. Inclusion criteria: term and post-term neonates weighing 2500 g or more with severe birth asphyxia. Severe birth asphyxia was defined by: Apgar score of ≤3 in first minute and ≤5 in the fifth minute, base deficit &gt;15 mEq/L in cord or arterial sample or need for severe resuscitation. Exclusion criteria: preterm delivery, small for gestational age, congenital anomalies, need for drugs affecting kidney function, hypotension, requirement of ventilator, seizures, cerebral attacks, severe kidney dysfunction and oliguria.</td>
<td>Experimental group received single intravenous dose of 5 mg/kg theophylline slowly. Placebo group received 2 mL of dextrose solution.</td>
<td>1. Acute kidney failure. 2. Serum and urinary creatinine. 3. GFR. 4. Urinary sodium excretion. 5. Serum electrolytes. Acute kidney failure was defined as: increase in serum creatinine ≥0.3 mg/dL or serum creatinine level &gt;1.5 mg/dL for at least two consecutive days.</td>
<td>Blinding of participants, caregiver and outcome assessor along with allocation concealment unclear. Theophylline levels not done.</td>
</tr>
<tr>
<td>Study author</td>
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<tr>
<td>Bhatt GC, et al.</td>
<td>Single centre, Iran</td>
<td>Numbers (n=22): aminophylline group (n=11); placebo group (n=11). Age: preterm neonates.</td>
<td>Experimental group: received single dose of aminophylline 5 mg/kg slowly. Placebo group received 5% dextrose water</td>
<td>1. Urine output. 2. GFR. 3. B2 microglobulin levels. 4. NAG levels.</td>
<td>Random sequence generation, blinding of participants, caregiver and outcome assessor along with allocation concealment unclear. Theophylline levels not measured.</td>
</tr>
<tr>
<td>Axelrod et al.</td>
<td>Single centre, USA</td>
<td>Numbers (n=144): aminophylline group (n=72); placebo group (n=72). Age: patients less than 18 years old with congenital heart defects undergoing cardiac surgery with cardiopulmonary bypass.</td>
<td>Experimental group received aminophylline 5 mg/kg intravenously over 30 min followed by 1.8 mg/kg intravenous every 6 hours for 72 hours (13 doses). Placebo group received intravenous infusion of normal saline for the same duration.</td>
<td>1. Development of AKI in the first five postoperative days. 2. Median time between postoperative CVICU admission and first successful endotracheal extubation. 3. Mean percentage fluid overload. 4. Total fluid balance. 5. Urine output. 6. Inotropic support.</td>
<td>Study drug was discontinued in 24% in experimental arm and 15% in placebo group (but intention-to-treat analysis was done). The trial has low risk of bias in all domains. Theophylline trough levels were measured.</td>
</tr>
<tr>
<td>Raina et al.</td>
<td>Single centre, India</td>
<td>Numbers (n=159): theophylline group (n=78); placebo group (n=81). Age: term neonates.</td>
<td>Experimental group received single dose of intravenous theophylline 5 mg/kg over 5 min period. Control group received equal volume of placebo (0.25 mL/kg normal saline).</td>
<td>1. Severe renal dysfunction. 2. Serum creatinine. 3. GFR. 4. Urinary sodium excretion. 5. Fluid balance.</td>
<td>Blinding of participants, caregiver and outcome assessor unclear. Follow-up not done. Theophylline levels were not measured.</td>
</tr>
<tr>
<td>Ghazala et al.</td>
<td>Single centre, Pakistan</td>
<td>Numbers (n=80): theophylline group (n=40); placebo group (n=40). Age: term neonates.</td>
<td>Experimental group received single dose of intravenous theophylline 5 mg/kg slowly. Control group received 2 mL/kg of 10% dextrose solution.</td>
<td>1. Severe renal dysfunction. 2. Serum creatinine. 3. Serum electrolyte. 4. Fluid balance. 5. Urine output.</td>
<td>Allocation concealment, blinding of participants, caregiver and outcome assessor as well as selective outcome reporting were unclear. The outcomes were not defined. Follow-up not done. Theophylline levels were not measured.</td>
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</table>

AAP, American Academy of Pediatrics; AKI, acute kidney injury; CVICU, cardiovascular intensive care unit; GFR, glomerular filtration rate; KDIGO, kidney disease improving global outcomes; NAG, N-acetyl-beta-D glucosaminidase; NICU, neonatal intensive care unit.
domains, and the rest seven trials have unclear risk of bias in one more domains (random sequence generation, allocation concealment, blinding and selective reporting) without any domain for high risk of bias (online supplementary figure 1).

The risk of bias for random sequence generation was unclear in three trials. The risk of bias for allocation concealment was unclear in five trials. The risk of performance bias was unclear in four trials. Reporting bias was low in all except one trial.

Theophylline versus placebo for prevention of AKI in term neonates with severe birth asphyxia

Theophylline was given in a single doses of 5mg/kg in four trials and 8mg/kg in two trials.

Primary outcome measures

1. Incidence of AKI: six trials with 436 participants reported this outcome. The pooled estimate showed 60% reduction in the incidence of AKI in the neonates with severe birth asphyxia receiving single dose of prophylactic theophylline compared with placebo (RR: 0.35; 95% CI 0.25 to 0.49; I²=0%) (figure 2).

2. Creatinine levels during initial 5 days: this outcome was reported by six trials. A high degree of unexplained heterogeneity was noted for this outcome. There was no significant difference between the creatinine levels on day 1 (mean difference (MD): −0.24; 95%CI −0.72 to 0.24; I²=98%). Over the next 2–5 days, there was a significant decrease in serum creatinine levels in neonates who received theophylline (day 5 level: [MD: −0.38; 95%CI −0.56 to −0.21; I²=83%]) (figure 3).

3. All-cause mortality: five trials with 356 participants reported 47 deaths. The pooled estimate showed 12% reduction of mortality in neonates who received prophylactic theophylline. However, the difference between the two groups was not significant (RR: 0.88; 95%CI 0.52 to 1.30; I²=0%) (figure 4).

Secondary outcome measures

1. Fluid balance during the initial 5 days: four trials reported this outcome, and the pooled estimate showed a significant negative fluid balance in the neonates who received a single dose of prophylactic theophylline as compared with placebo. There was no significant difference between the two groups on day 1 (MD: −0.22, 95%CI −0.51 to 0.08; I²=95%), day 2 (MD: 0.79; 95%CI 0.04 to 1.53; I²=96%) and day 4 (MD: 0.20, 95%CI −0.22 to 0.62; I²=89%). However, the difference was significant on day 3 (MD: 0.5; 95%CI 0.11 to 0.89; I²=86%) and day 5 (MD: 0.32; 95%CI 0.20 to 0.44; I²=34%). Another trial reported a negative fluid balance in favour of the theophylline group over days 2–5 compared with placebo (figure 5 and online supplementary figure 2).

2. eGFR during the initial 5 days: four trials reported this outcome. Although there was no significant difference in the eGFR on days 1 (MD: 1.17; 95%CI −2.8 to 5.16; I²=47%) and 4 (MD: 3.9; 95%CI −13.9 to 21.8; I²=96%), the difference was significant on days 2 (MD: 9.4; 95%CI 6.1 to 12.8; I²=0%), 3 (MD: 14.3; 95%CI 11.73 to 16.87; I²=0%) and 5 (MD: 10.1; 95%CI 5.81 to 14.29; I²=47%) (online supplementary figure 3).

3. Urinary β2 globulin levels during the initial 5 days: three trials reported this outcome. The pooled results showed significantly lower mean urine β2 microglobulin (B2M) concentrations, used as a marker of tubular injury, in the treatment group compared with the control (MD: −7.07; 95%CI −8.93 to −5.22; I²=32%) (online supplementary figure 4).

4. Complications: five trials reported this outcome (online supplementary figure 5).

Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. CKD, chronic kidney disease.

Figure 2 Forest plot showing incidence of AKI in neonates with severe birth asphyxia (theophylline vs placebo). AKI, acute kidney injury.
a. Requirement of ventilatory support: two trials with 195 participants reported this outcome. There was no significant difference between treatment and control group (RR: 0.75; 95% CI 0.43 to 1.31; I²=44%).

b. Requirement of inotropic support: four trials9 10 12 13 with 320 participants reported this outcome without significant difference between groups (RR: 0.92; 95% CI 0.68 to 1.25; I²=0%).

c. Seizures: four trials9 11–13 with 286 participants reported this outcome without significant difference between groups (RR: 0.79; 95% CI 0.56 to 1.12; I²=0%).

### Theophylline for preterm infants with respiratory distress syndrome

We identified a single, double-blind randomised, placebo controlled trial examining the effect of intravenous theophylline in preterm neonates with respiratory distress syndrome at a dose of 1 mg/kg for 3 days.17 The incidence of oliguria was decreased in preterm neonates receiving theophylline on day 1 (RR: 0.14; 95% CI 0.02 to 1.05), but the difference did not extend to the subsequent 10 days. Serum creatinine levels on day 24 were insignificantly lower in neonates who received theophylline compared with placebo (MD: −22.50; 95% CI −39.25 to 5.75). Similarly, creatinine levels on days 3 to 10 did not differ significantly between groups. All-cause mortality and other secondary outcomes were not reported.

### Aminophylline for preterm neonates with perinatal asphyxia

One trial examined the effect of a single dose of aminophylline on renal function and markers of AKI (N-acetyl-glucosaminidase and B2M) on days 1, 4 and 7 of life.14 Aminophylline (5 mg/kg) was given to preterm neonates with perinatal asphyxia(n=11)
within the first hour after birth and compared with placebo (n=11). Aminophylline-treated infants demonstrated significantly higher eGFR on day 4 compared with placebo with no difference in NAG and B2M levels and increased urine output from day 1. Incidence of AKI, all-cause mortality and other secondary outcomes were not reported.

Aminophylline for children less than 18 years with congenital heart defects undergoing cardiac surgery

One trial reported use of aminophylline in postoperative children after congenital heart surgery with cardiopulmonary bypass.15 This was a double-blind randomised placebo controlled trial where the experimental group (n=72) received intravenous aminophylline (5 mg/kg loading dose followed by 1.8 mg/kg every 6 hours for 72 hours) (n=72) and the control group isotonic saline (placebo) matched by volume and appearance. Study drug was discontinued in 24% of the patients in the experimental arm and 15% of subjects in the placebo group. There was no difference in the incidence and stage of serum creatinine-based AKI or urine output between the two groups. A subgroup analysis (<3 months old) showed no difference between the outcomes, but this analysis was insufficiently powered. Adverse event rates were similar in both groups.

**Treatment emergent adverse events**

These were reported in seven of nine trials. They were mainly related to the disease process and occurred with similar frequency in either group. Table 2 shows treatment emergent adverse events and whether the treatment emergent adverse events were defined as one of the outcomes.

**Sensitivity analysis**

As all the six included trials of theophylline versus placebo for prevention of AKI in neonates with severe birth asphyxia were having one or more domains of unclear risk of bias, we could not perform sensitive analysis.

**Publication bias and small effect**

Due to the paucity of published studies (<10), a funnel plot was not constructed.

**Grade of evidence**

The grade evidence generated for the comparison of theophylline versus placebo for prevention of AKI in neonates with birth asphyxia was as follows: ‘moderate’ quality for incidence of AKI/severe renal dysfunction, and ‘very low’ to ‘low’ quality for serum creatinine levels on days 1–5 and all-cause mortality (table 3). This was because of serious study limitations (unclear risk of bias in one or more domains of random sequence generation, allocation concealment, blinding and selective reporting), a very high and statistically significant heterogeneity and the 95% CI includes null effect and/or appreciable benefit or harm.
## Table 2 Summary of adverse events in the included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of collection of adverse effect data</th>
<th>Priori inclusion of adverse effects in primary/secondary outcomes</th>
<th>Adverse effects or complications reported*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenik et al13</td>
<td>Routine monitoring.</td>
<td>Not mentioned.</td>
<td>13/27 infants in control group and 9/24 in theophylline group developed seizures. Authors stated no difference in frequency and severity of CNS, pulmonary, heart and gastrointestinal involvement.</td>
</tr>
<tr>
<td>Bhat et al10</td>
<td>Routine monitoring.</td>
<td>Not mentioned.</td>
<td>Author stated, ‘No side effects occurs in infants receiving theophylline’. Figure showed no significant involvement of CNS, cardiac or GIT between the two groups.</td>
</tr>
<tr>
<td>Cattarelli et al17</td>
<td>Routine monitoring.</td>
<td>Yes. Complications such as PDA, intraventricular haemorrhage, PVL, ROP, BPD and NEC were considered.</td>
<td>PDA: 6/24 in placebo and 3/23 in theophylline group. PVL: 2/24 in placebo and 2/23 in theophylline group. ROP: 2/24 in placebo and 2/23 in theophylline group. BPD: 4/24 in placebo and 1/23 in theophylline group. NEC: 1/24 in placebo and 0/23 in theophylline group.</td>
</tr>
<tr>
<td>Merrikhi et al4</td>
<td>Questionnaire (whether the questionnaire contained items for adverse events not mentioned).</td>
<td>Not mentioned.</td>
<td>No.</td>
</tr>
<tr>
<td>Axelrod et al15</td>
<td>Routine monitoring.</td>
<td>Patients with history of seizures, tachyarrhythmias and liver dysfunction were excluded. Trial was monitored by data safety monitoring board with access to unblinded data. No prior inclusion of adverse event in method section.</td>
<td>Eleven adverse events occurred in 10 patients in the treatment group and 13 adverse events occurred in 13 patients in the placebo group.</td>
</tr>
<tr>
<td>Raina et al9</td>
<td>Routine monitoring.</td>
<td>Not mentioned.</td>
<td>Seizures: 10/81 in placebo group and 9/78 in theophylline group. Authors stated, ‘No major differences in CNS, pulmonology, GIT or cardiac were observed between two groups. No adverse effects attributable to theophylline occurred in the intervention group’.</td>
</tr>
</tbody>
</table>

*Includes both authors’ attempt to detect adverse events as well as complications related to disease process.

BPD: bronchopulmonary dysplasia; CNS, central nervous system; GIT, gastrointestinal tract; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

## DISCUSSION

### Summary of evidence

An extensive literature search in the present systematic review revealed nine trials to be eligible for inclusion. Of these, the data from six trials enrolling 436 neonates who were given prophylactic theophylline as compared with placebo were meta-analysed. The findings of the present systematic review indicate that single dose of prophylactic theophylline given to term neonates increases the mortality to as high as 60%, especially in neonates with low Apgar score at 5 min, oliguria and fluid overload of more than 20%.31 32

A recent trial9 that recruited 159 severely asphyxiated term neonates showed that the neonates receiving single prophylactic dose of theophylline had a lower creatinine levels, had higher creatinine clearance and significantly decreased risk of AKI/severe dysfunction. The authors also found a lower mortality rate in the neonates who received prophylactic theophylline, though the difference was not statistically significant. A secondary analysis from the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study found that caffeine administration in preterm neonates was associated with reduced incidence and severity of AKI.33

Experimental studies in animals have shown that renal adenosine act as a vasoconstrictive metabolite in the kidney after hypoxia causing fall in GFR and filtration factor.34 Thus, non-specific adenosine receptor antagonists such as theophylline inhibits vasoconstriction produced by adenosine. Another experimental study using 8-cyclopentyl-1,3-dipropylxanthine, a specific antagonist of the A1 adenosine receptors found it to be less effective than theophylline in preventing hypoxia-induced renal failure, thus implicating that the later agent may act on the other targets than adenosine A1 receptors.35

Theophylline has wide variation in metabolism and a narrow therapeutic window, and hence, it is essential to measure theophylline levels to avoid toxicity.36 Only three13 15 17 of nine included studies...
The authors would like to thank Dr Nishant P Jaiswal, Scientist C, Indian Council of Medical Research (ICMR) Advanced Centre for Evidence Based Child Health, PGIMER, Chandigarh, for his help in the database search. GCB was supported by the ICMR International Fellowship award.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

Original article


