Aminophylline for improving acute kidney injury in pediatric patients: A systematic review and meta-analysis

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ABSTRACT

Objectives: Acute kidney injury (AKI) is a major cause of morbidity and mortality. Whether aminophylline administration can prevent or treat AKI among pediatric patients are not clear. This meta-analysis aimed to assess the efficacy and effectiveness of aminophylline for pediatric AKI.

Methods: We carried out a systematic search of six databases: PubMed, EMBASE/Excerpta Medica, Scopus, Cochrane library, and Google Scholar from January 1995 up till May 2019. Summary measures of risk ratios and standard mean difference were calculated using the random effects model.

Results: We identified seven papers containing data on aminophylline use in children with AKI. Meta-analysis of single-arm studies indicated no statistically significant difference in mean rate of serum creatinine clearance (−0.39 [−0.80–1.58], $P = 0.52$), mean urine output (1.99 [−1.43–5.42]; $P = 0.25$), or mean blood urea nitrogen levels (0.83 [−1.86–3.03], $P = 0.54$) before and after aminophylline administration. However, among double-arm studies, aminophylline administration in the intervention arm significantly reduced the serum creatinine level as compared to control arm (mean diff = −34 [−55.18−−12.83]; $P = 0.002$). Mean urine output (−112.68 [−27.43–48.9], $P = 0.17$), incidence of AKI (RR = 1.05 [0.80–1.37], $P = 0.72$), and mortality rates (RR = 0.79 [0.42–1.47], $P = 0.45$) were found to be statistically insignificant.

Conclusions: Aminophylline administration in children with AKI reduces serum creatinine level without significant adverse effects or effect on the incidence of AKI, urine output, or mortality. Further, large-scale well-planned randomized controlled trials are needed to evaluate its use and its potential long-term effects.

Keywords: Aminophylline, pediatric patients, acute kidney injury, renal outcomes, efficacy

Introduction

Acute kidney injury (AKI) has been defined as the sudden reduction in the kidney functions leading to reduced glomerular filtration rate (GFR). It occurs as a consequence of a few major diseases, major surgeries such as cardiac surgery and sepsis among all age groups. However, the condition is much more serious and difficult to control among children.[1,2] The incidence of AKI ranges from 28 to 51% among children, 52% in infants (<90 days), and 64% in neonates (aged ≤6 weeks) who underwent surgery for congenital heart defects such as biventricular cardiac repairs and cardiopulmonary bypass, resulting in high morbidity and mortality.[3-5] Serum creatinine is a traditional marker of renal function; however, it does not rise before 50% loss of renal function.[6] A minor rise in serum creatinine levels can seriously impact the socioeconomic status of a family by increasing length of hospital stay, greater hospital cost, prolonged need for mechanical ventilation, and increased mortality.[1,3,6,7]

There are two possible pathways of the complications developed by a pediatric patient after the first episode of AKI. One pathway hypothesizes that the survivors after the first attack of AKI would fully recover without having adverse effects in the future.[2,8] However, a recent meta-analysis has confirmed an increased risk of proteinuria, hypertension, and GFR <90 mL/min/1.73 m^2 as a long-term complication after the first episode of AKI. This evidence reinforces the need to properly manage first episode of AKI effectively so as to reduce future morbidities.[2,8]

Various classes of drugs have undergone randomized controlled trials (RCTs) to assess their effectiveness in the prevention

and/or treatment of AKI in children. Some these medications include diuretics (furosemide), dopamine, fenoldopam, theophylline/aminophylline, and rasburicase. Furosemide is a widely used diuretic for increasing the urine outflow but it has not shown any effect on prevention or treatment of pediatric AKI.[9,10] Similarly, dopamine and another dopamine receptor agonist fenoldopam have initially showed promising results in animal models but failed to prevent or treat AKI in clinical trials among humans.[11] Recently, studies have suggested the potential beneficial effects of methylxanthines such as theophylline and aminophylline in both the prevention and treatment of AKI.[12-24] In animal studies, theophylline – an adenosine receptor antagonist – was found to be protective of kidney injury following ischemia in rodents.[12-13] Furthermore, two meta-analyses have shown that theophylline was useful in the prevention of contrast-induced nephropathy and another meta-analysis noted an over 50% reduction in the risk of contrast-induced nephropathy-related AKI with the use of theophylline.[14-16] Similarly, several case series, case reports, and observational studies have suggested that the non-selective adenosine antagonist aminophylline was beneficial in both the prevention and treatment of pediatric AKI following cardiac surgeries or in critically ill children.[17-25] However, some of the recently published randomized clinical trials have shown inconsistent finding of its benefits.[26,27]

A few systematic reviews and meta-analyses have been conducted to assess the effects of methylxanthines and other medications for the improvement in or reduction of AKI in children.[29-31] However, most of these focused mainly on the effects of theophylline or other pharmacological measures such as dexmedetomidine, acetaminophen, and fenoldopam with limited evaluation of the effects of aminophylline.[29-31] We conducted this systematic review and meta-analysis to explore the present evidence and summarize the effects of aminophylline for the prevention and/or treatment of AKI among pediatric patients aged <18 years. The review specifically assessed the efficacy and safety of aminophylline compared with standard therapy or placebo for pediatric AKI prevention and/or treatment in terms of its effect on serum creatinine clearance rate, urine output, incidence of AKI, and mortality rate.

Methods

We have performed this meta-analysis as per the standard guidelines of Cochrane Collaboration. We followed the Preferred Reporting Items for Systematic Reviews and Meta- analyses and Meta-analysis of Observational Studies in Epidemiology guidelines for reporting systematic review and meta-analysis of RCTs and observational studies.[32,33]

Study population/exposure group

Pediatric patients (between the age of 0 and 18 years) having AKI or at increased risk of developing AKI.

Operational definitions

Increased risk of developing AKI: This term refers to the pediatric patients who did not have AKI preoperatively but had high chances of developing it after a major surgery like cardiac surgery or after sepsis. The definition of AKI in this study was based on the definition used by the included studies.

Interventions to be compared

Intervention arm

Aminophylline administered among pediatric patients who have/had AKI or increased risk of developing AKI.

Control arm

Non-aminophylline arm where either some other drug or standard therapy other than aminophylline was administered or no drug was administered (placebo). We excluded children with preexisting acute or chronic kidney disease and children with seizures and cardiac complications.

Study selection

Types of study

We included all RCTs as well as single-arm trials from January 1995 up till May 2019. Due to limited literature examining the effects of aminophylline, we also included relevant single-arm observational studies and case series.

However, we summarized the findings of single-arm observational studies and case series separately from RCTs to allow for meaningful interpretation of the findings. This approach allowed us to strengthen the evidence base in a research area with scarcity of well-planned double-armed RCTs which are considered to be the highest level of evidence-based studies.

Study selection

The following data sources were searched for all RCTs and prospective cohort control studies: PubMed, EMBASE/ Excerpta Medica, SCOPUS, Cochrane Central Register of Controlled Trials, Google Scholar, and reference lists of relevant publications. The search strategies were independently designed and performed by two separate investigators (SA and SB). We used the following MeSH terms or keywords in different combinations and permutations to perform the search and limited our search to studies published from January 1995 to May 2019 without language restriction in the selected databases:

"AKI," "Acute kidney failure," "Aminophylline," "pediatric patients," and "children."

The search strategies described above provided a list of studies. The titles and abstracts of all the retrieved studies were screened independently by two of the investigators (SA and SB). The irrelevant studies were discarded in the first screen

of the titles and abstracts after removing duplicate articles. Subsequently, the full text of the selected studies was analyzed for the presence of outcome measures of interest.

Primary outcome measures

1. Serum creatinine clearance rate
2. Urine output rate
3. Incidence of developing AKI
4. Mortality rate.

Data extraction

The data were extracted using a pilot tested pro forma designed for the review. Two of the investigators (SA and SB) independently extracted data. The following information were extracted from the selected studies: First author, publication year, country, number of participants in each group, patient profile, intervention therapy details along with clearance rates of serum creatinine, rate of urine output, incidence of developing AKI, and mortality rates among the intervention and control groups. Outcomes reported in two or more articles were extracted for meta-analysis.

Data analysis

Extracted data were entered and analyzed using Revman 5.3. Before the analysis, data were standardized into equivalent units. Dichotomous variables AKI incidence and mortality rates in the aminophylline and non-aminophylline arms were expressed as rate ratio with 95% confidence interval (CI). For continuous variables such as serum creatinine clearance rate and urine output rate, standardized mean difference and 95% CI were calculated for each study. Pooled estimates were determined using the random effects model. Heterogeneity in the studies was evaluated using the Cochrane Q test and I^2 statistic to assess the degree of interstudy variation. I^2 values of 0%–24.9%, 25%–49.9%, 50%–74.9%, and 75%–100% were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity.

Ethical considerations

Ethical approval was not required for this study as it involved data extraction and data summation of the studies, which had already been conducted. These studies had already sought ethical approval and informed consent from the institute and the study participants.

Results

Section A. Study selection and description

The combined literature search identified around 1500 relevant studies, which contained the MeSH terms either in the title or abstract. Following the removal of duplicate studies (126) and a detailed review of the titles and abstracts; we included 18 studies for full-text review. Finally, only seven studies matched the inclusion criteria. The excluded studies were rejected on various grounds described in Figure 1.

The eligible studies were conducted from year 2000 till 2016. Out of totals even eligible studies, there was four single-arm trials or case series, as depicted in Table 1.[19,21,22,25] These studies did not have any comparison group and were, therefore, analyzed them separately. These single-arm trials were carried out using varied methodologies like the one done by McLaughlin *et al.* was a retrospective observational study, whereas Axelrod *et al.* documented a retrospective cohort study, as depicted in Table 1.[22,26] Lynch *et al.* and Tamburro *et al.* documented a case series to evaluating the effectiveness of aminophylline.[21,25] The total sample size was 89 with mean age ranging from 24 weeks to 3.8 years.

The other three studies had the comparison group but again, followed different methodologies.[23,24,26] Of these two are retrospective cohort studies and one was a RCT. The total sample size for these three studies was 361. All the three studies had similar intervention arm but different control arm as shown in Table 2. Two of the studies were conducted among children who underwent cardiovascular surgery.

Section B: Analysis of single arm studies

Outcome 1: Rate of serum creatinine clearance
The summary mean difference of all studies[19,21,22,25] indicated that there was no significant difference in the mean creatinine clearance rate among pediatric patients before and after the administration of aminophylline (mean difference = 0.39, 95% CI = −0.80-1.58, P = 0.52), Figure 2. There was significant heterogeneity among the selected studies for this outcome measure ($\tau2$ = 1.27, Chi-square = 34.65, df = 3, P < 0.00001, I^2 = 91%).

Outcome 2: Rate of urine output
Only two studies carried out by Tamburro *et al.* and McLaughlin *et al.* documented the rate of urinary output before and after
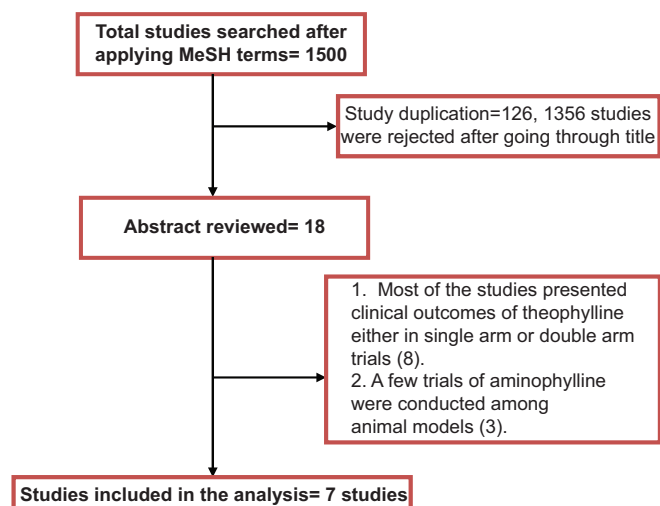

Total studies searched after applying MeSH terms= 1500

Study duplication=126, 1356 studies were rejected after going through title

Abstract reviewed= 18

1. Most of the studies presented clinical outcomes of theophylline either in single arm or double arm trials (8).
2. A few trials of aminophylline were conducted among animal models (3).

Studies included in the analysis= 7 studies

Figure 1: Flowchart showing selection of studies

Table 1: Matrix of single-arm studies

First author, year	Design	Country	Study period	Total sample size	Mean age	Male %	Patient disease profile	Group 2 (after) dose of aminophylline
McLaughlin *et al.*, 2000	Retrospective observational	Miami	NA	10	2.8 years	NA	Children with tacrolimus-induced renal insufficiency	NA
Lynch *et al.*, 2008	Retrospective case series	North Carolina	15 months	13	24–40 weeks	NA	Neonates with acute renal failure	1 mg/kg intravenously or orally every 12 h
Axelrod *et al.*, 2014	Retrospective cohort	Scotland	7 days	31	3.8 years	52	Children with congenital or acquired heart disease	52 courses of aminophylline
Tamburro *et al.*, 2014	Prospective single-arm trial	USA	24 h	35	5.1–11.5 months	66	Pediatric ICU	NA

Table 2: Matrix of double-arm studies

First author, year	Design	Country	Study period	Total sample size	Intervention arm sample size	Control arm sample size	Mean age	Male %	Patient disease profile	Intervention arm drug dosage	Control arm drug dosage
Axelrod *et al.*, 2016	RCT	Stanford	5 days	144	72	72	2.3 years	56	Cardiovascular surgery	Aminophylline 6 hourly over 72 h	Normal saline 6 hourly over 72 h
Onder *et al.*, 2016	Retrospective cohort	West Virginia	69 months	200	100	100		60	Children with congenital heart disease in PICU	Aminophylline.	Furosemide
Olowu *et al.*, 2012	Retrospective observational	Nigeria	NA	17	9	8	4.6–4.9 years	NA	Children with oliguric/anuric kidney injury	Aminophylline	Placebo
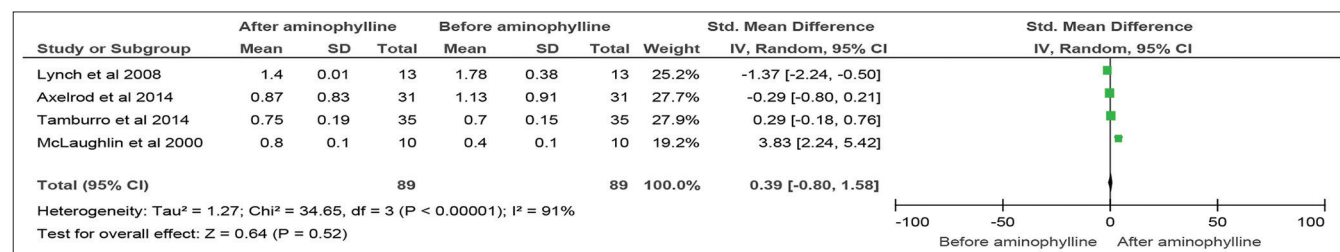
Figure 2: Forest plot comparing serum creatinine clearance rate before and after aminophylline administration among pediatric patients

administering aminophylline.[22,25] It was found that there was no significant difference in the mean rate of urinary output among pediatric patients before and after the administration of aminophylline (mean difference = 1.99, 95% CI = −1.43-5.42, P = 0.52), Figure 3. There was also significant heterogeneity among the selected studies for this outcome measure ($\tau2$ = 5.77, Chi-square = 17.15, df = 1, P < 0.00001, I^2 = 94%).

Outcome 3: Difference in mean blood urea nitrogen (BUN) levels

The summary measures of two studies[21,25] indicated that there was no significant difference in the BUN clearance rate among pediatric patients before and after the administration of aminophylline (mean difference = 0.83, 95% CI = −1.86-3.53, P = 0.54), Figure 4. There was significant heterogeneity among the selected studies for this outcome measure ($\tau2$ = 3.62, Chi-square = 23.14, df = 1, P < 0.00001, I^2 = 96%).

Section C: Analysis of double arm studies

Outcome 1: Comparing mean serum creatinine concentration among intervention and control arm

All the three studies provided data to analyze this outcome measure.[23,24,26] The summary mean difference of all studies indicated that there was significant reduction in the mean serum creatinine concentration among pediatric patients who were administered aminophylline as compared to control group (mean difference = −0.34, 95% CI = −55.18–−12.83, P = 0.002), Figure 5. There was significant heterogeneity among the selected studies for this outcome measure ($\tau2$ = 233.45, Chi-square = 43.67, df = 3, P < 0.00001, I^2 = 95%).

Outcome 2: Comparing mean urine output among intervention and control arm

All the three studies provided data to analyze this outcome measure.[23,24,26] The summary mean difference of all studies

indicated that there was no significant improvement in the urinary output among pediatric patients who were administered aminophylline as compared to control group (mean difference = −112.68, 95% CI = −274.26–48.90, $P = 0.17$), Figure 6. There was 100% heterogeneity among the selected studies for this outcome measure (Chi-square = 416.08, df = 3, $P < 0.00001$, $I^2 = 100\%$).

Outcome 3: Comparing AKI among intervention and control arm

The summary risk ratio of all studies[23,24,26] indicated that there was no significant difference in the incidence rate of AKI among pediatric patients who were administered aminophylline as compared to control group (RR = 1.05, 95% CI = 0.80–1.37, $P = 0.72$). Figure 7. There was 56% heterogeneity among the selected studies for this outcome measure (Chi-square = 4.52, df = 2, $P = 0.10$, $I^2 = 56\%$).

### Outcome 4: Comparing incidence of mortality rate among intervention and control arm

The summary risk ratio of all studies[23,24] indicated that there was no significant difference in the mortality rates among pediatric patients who were administered aminophylline as compared to control group (RR = 0.79, 95% CI = 0.42–1.47, $P = 0.45$), Figure 8. There was no heterogeneity among the selected studies for this outcome measure (Chi-square = 0.56, df = 2, $P = 0.45$, $I^2 = 0\%$).
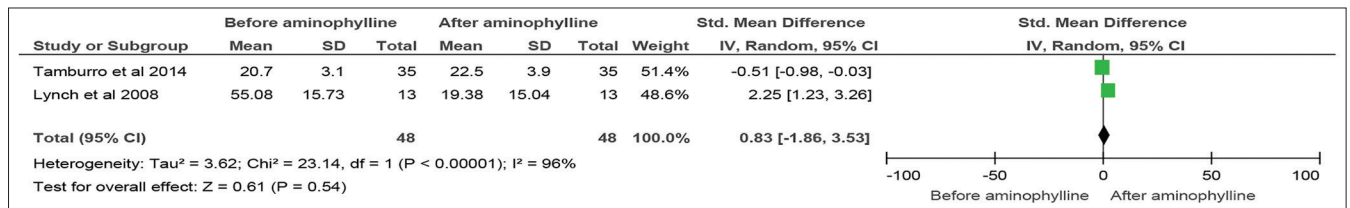
Discussion

Summary of main findings

The present meta-analysis was performed to systematically summarize the available evidence and assess the effectiveness of aminophylline in preventing and/or treating AKI induced
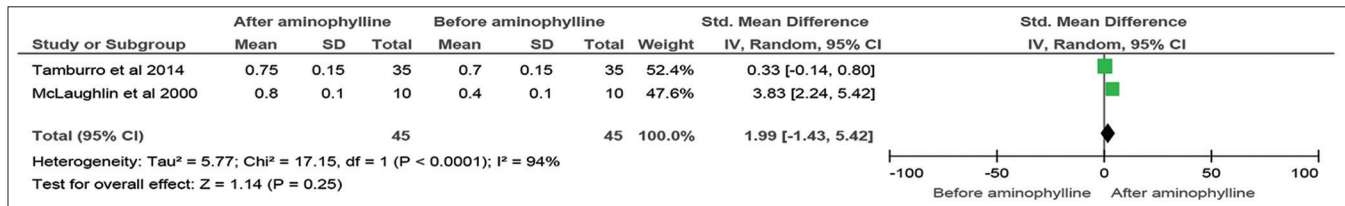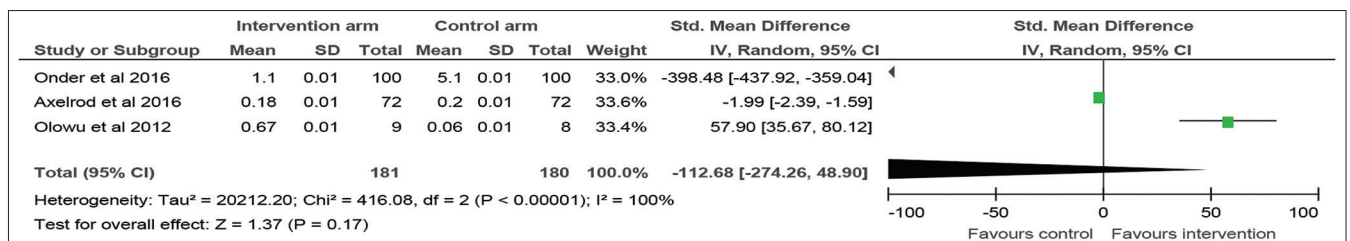

Figure 3: Forest plot comparing urine output rate before and after aminophylline administration among pediatric patients

Figure 4: Forest plot comparing mean BUN clearance levels before and after aminophylline administration among pediatric patients
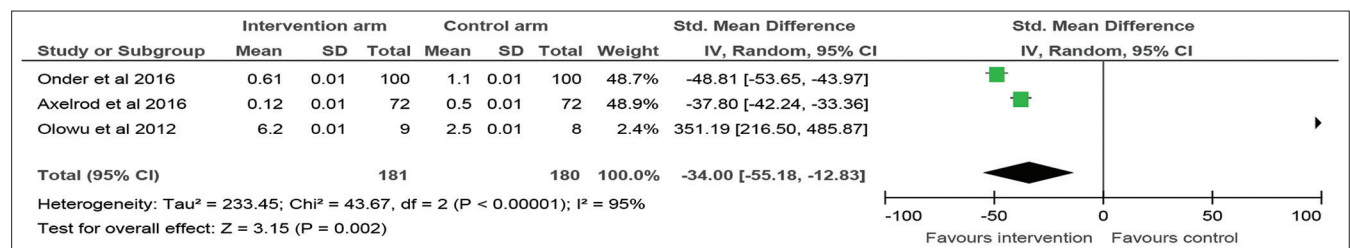
Figure 5: Forest plot comparing change in serum creatinine concentration among aminophylline administration group versus control group among pediatric patients

Figure 6: Forest plot comparing mean urinary output among aminophylline administration group versus control group among pediatric patients
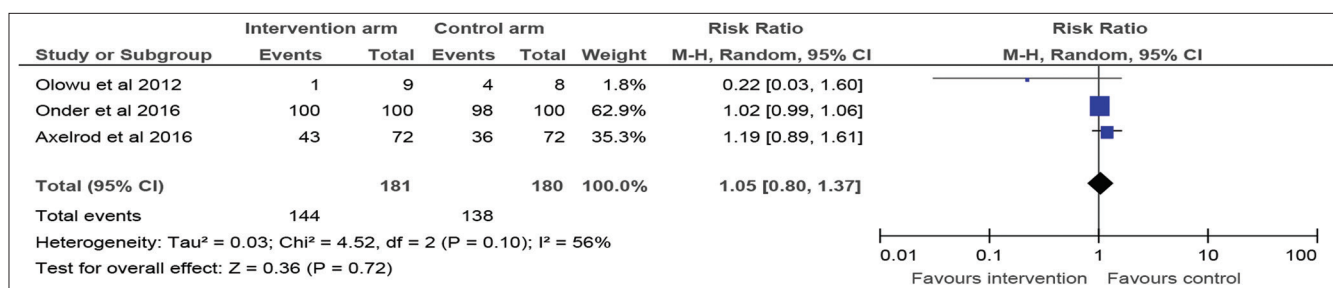
Figure 7: Forest plot comparing acute kidney injury among aminophylline administration group versus control group among pediatric patients
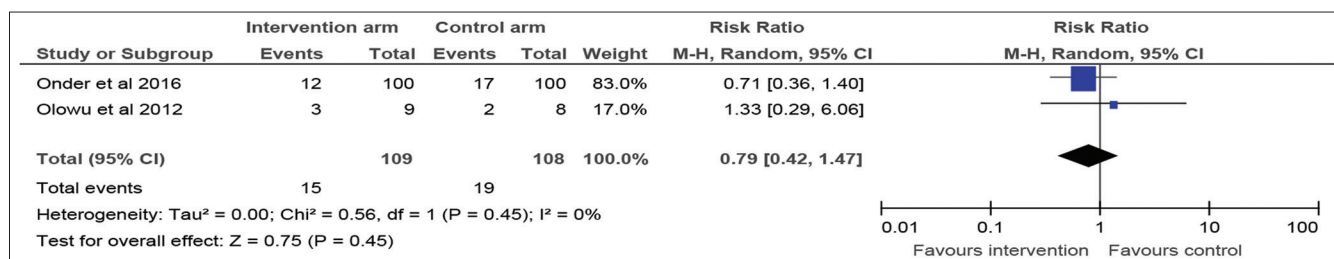

Figure 8: Forest plot comparing mortality rate among aminophylline administration group versus control group among pediatric patients

by a major surgery or illness in pediatric patients. We found only seven studies which were either single-arm observational studies or clinical trials. Outcomes of the meta-analysis revealed that there were no significant effects of aminophylline use on the incidence of AKI, serum creatinine clearance rate, urine output, and all-cause mortality in the single-arm studies. While in the double-arm studies, except for serum creatinine clearance, similar findings were observed. This approach adopted to perform this review enabled us to pool data from all available studies irrespective of the study design. Hence, this may be considered as a strength of this meta-analysis which has summarized data on the effectiveness of aminophylline use from both clinical trials, observational studies and case series.

In our study, the analysis of single-arm studies or case series suggested that there is no difference in the mean creatinine clearance rate, mean urinary output, and mean BUN levels before and after the administration of aminophylline among pediatric patients. Similarly, except for the mean change in the serum creatinine level, the results were statistically insignificant for other outcomes in double-arm trials.[23,24,26] The findings of this meta-analysis are in line with the individual studies included in this analysis. Furthermore, although the standardized mean difference in urinary output increased following the administration of aminophylline, the increase did not reach statistical significance. This finding may be due to the relatively small sample sizes of the included studies and these studies may not have enough power to detect the real difference or effects. Furthermore, there was substantial heterogeneity among the studies because of varied population attributes due to different age groups, geographical distribution, clinical conditions, different type of surgeries, and, importantly, different times of administering aminophylline. For instance, Axelrod *et al.* administered aminophylline to the

intervention group after 4 h postoperatively following cardiac surgery among children having mean age of 2.3 years,[26] while Onder *et al.* administered aminophylline intraoperatively during cardiac surgery among pediatric patients.[24]

The findings of this systematic review suggest that the use of aminophylline in children has minimal effect in the prevention or treatment of AKI, creatinine concentrations, urine output, and mortality. Although, some of the findings of the individual studies suggested that the medication may have an effect in improving renal perfusion,[19,21-26] and some of these outcomes, their pooled analysis indicated limited effects on the outcomes. A previous study has suggested that renal tissue response may be age dependent; but this needs to confirmed in future large-scale studies.[28] Pooled analysis from studies having a control group indicates that aminophylline use was associated with significant reduction in the mean serum creatinine concentration.[23,24,26]

The mechanisms of action of aminophylline in lowering serum creatinine clearance and possibly improving renal perfusion could be explained by adenosine receptor inhibition at minimal doses and type IV phosphodiesterase blockade at increased doses. Adenosine plays an important role in tubuloglomerular feedback.[34] With increasing solute load in the renal tubules, energy depletion occurs, accompanied by the release of adenosine. The secreted adenosine stimulates pre-glomerular vasoconstriction leading to a reduction in solute flow and, contributing to, maintaining energy balance. Furthermore, aminophylline-induced phosphodiesterase inhibition lowers the breakdown of cAMP, which promotes renal vasodilation and renal perfusion.[35] Despite the divergent results of the effects of aminophylline, substantial interest still exists in the evaluation of the effect of aminophylline for AKI. The Pharmacology of Aminophylline for AKI in Neonates

(PAANS) trial (NCT02276170) is currently underway and aims to explore the role of aminophylline as a treatment for AKI by measuring changes in urine output, creatinine, and other urine biomarkers among neonates.[36]

Limitations

This review has some strengths and limitations. This is an updated systematic review consisting of all studies irrespective of design which summarized the effect of aminophylline for AKI prevention or treatment in children. However, the review has some limitations. First, we found that most of the studies included in the review had small sample sizes and therefore insufficient power to detect differences in the outcomes. Second, there was substantial heterogeneity between the studies. This might have arisen from variations in the population attributes such as different age groups, geographical spread, clinical presentation, type of surgeries, and timing of administration aminophylline.[19,21-26] Finally, none of the studies assessed the long-term effect of use of aminophylline in children with AKI. Despite these limitations, this review has provided evidence to further justify the need for well-designed RCTs such as the ongoing neonates (PAANS) trial to assess the effectiveness of aminophylline for AKI in children.

Conclusions

This meta-analysis showed that aminophylline administration in children with AKI reduces the serum creatinine level without significant adverse effects or effect on the incidence of AKI, urine output, or mortality. Further well-designed trials reporting on all the outcomes are needed to assess the effectiveness of aminophylline in improving the renal outcomes of children with AKI or those at increased risk of developing it.

Author Declaration Statements

Ethical approval

Not applicable.

Statement of informed consent

Not applicable.

Availability of data and materials

Available with the corresponding author and will be produced on reasonable request.

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Interests of competing

None.

Authors' contributions

All authors equally contributed.

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