Electronic Journal of General Medicine
2023, 20(2), em448
e-ISSN: 2516-3507
https://www.ejgm.co.uk/

MODESTUM

Review Article

OPEN ACCESS

Cardiac surgery-associated acute kidney injury in newborns: A meta-analysis

Bekzat Suieubekov [1*], Anar Sepbayeva [1], Ainur Yeshmanova [1], Adilet Kusainov [2]

[1] Asfendiyarov Kazakh National Medical University, Almaty, KAZAKHSTAN
[2] Kazakh-Russian Medical University, Almaty, KAZAKHSTAN
*Corresponding Author: backzad.s12@gmail.com

Citation: Suieubekov B, Sepbayeva A, Yeshmanova A, Kusainov A. Cardiac surgery-associated acute kidney injury in newborns: A meta-analysis. Electron J Gen Med. 2023;20(2):em448. https://doi.org/10.29333/ejgm/12805

ARTICLE INFO

Received: 24 Oct. 2022

Accepted: 21 Dec. 2022

ABSTRACT

Introduction: Acute kidney injury is a common complication following pediatric heart surgery, and it has been linked to an increased risk of morbidity and fatality.

Methods: The PubMed and Medline databases were combed for relevant research until May 2022. The terms [Cardiac surgery] AND [acute renal injury] AND [newborns OR children OR neonates] AND [randomized control studies OR randomized control trials] were used as search criteria. The studies that met the inclusion criteria were considered qualified using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Results: A total of 2,941 newborns or children were enrolled in 14 studies, with 931 developing acute renal damage. 2,095 of the enrolled infants and children received steroid, aminophylline, dexmedetomidine, and acetaminophen therapies. In seven studies, the odds ratio for steroids was not significantly different from control. In contrast, two studies comparing aminophylline to a control group found no statistically significant change. Two studies found no significant difference in dexmedetomidine therapy compared to control. Three trials, however, found a significant difference between the acetaminophen treatment and control groups.

Conclusion: Acetaminophen was linked to a decreased risk of postoperative acute renal injury, while steroids had no benefit and aminophylline treatment could be justified.

Keywords: acute kidney injury, newborns, cardiac surgery, serum creatinine

INTRODUCTION

Acute kidney injury in infants is prevalent following heart surgery. It's a condition marked by a rapid decline of kidney function, as evidenced by a lower glomerular filtration rate and >50% increase in serum creatinine [1]. In contemporary clinical practice, however, there are two separate classifications for acute kidney damage in children based on blood creatinine levels and urine output: pediatric risk, injury, failure, loss, and end stage (pRIFLE) [2] and acute kidney injury network (AKIN) criteria [3]. Acute kidney injury after pediatric heart surgery affects 9.6% to 52% of children [4-10]. The high variability in the incidence rate is due to the type of surgical treatment performed, which can range from 94% in heart transplantation to 3% in thoracic surgery [11].

It is now well understood that the risk of acute renal injury increases as the age of the child undergoing surgery drops, with the risk in newborns reaching 50% to 60%, depending on the complications of the surgery. Other patient and procedure-related risk variables have also been identified, as shown in **Figure 1**. Other serum and urine indicators have been utilized in various trials to diagnose acute renal damage early [12]. As functional indicators, serum cystatin-C and urinary neutrophil gelatinase associated lipocalin (NGAL) have grown popular [13]. Brain natriuretic peptides, interleukin 6 and 18, kidney injury molecule 1, liver fatty acid binding protein, homovanillic acid sulfate, etc. are other biomarkers as shown in **Figure 1**.

The exact mechanisms of acute renal damage following heart surgery are unknown. Several investigations, however, have revealed that the causes are multifaceted. Cardiopulmonary bypass, neurohormonal variables, ischemic-reperfusion injury, nephrotoxins, oxidative stress, and inflammation are only a few of them [17]. Due to the specific physiology and underlying procedures required in heart surgery, such as aortic cross-clamping and cardiopulmonary bypass, as well as the need of frequent transfusions and vasopressors, patients undergoing cardiac surgery are particularly vulnerable [17]. Hemolysis is caused by the cardiopulmonary bypass circuit, which releases free hemoglobin and iron. Free hemoglobin depletes circulating haptoglobin and binds to Tamm-Horsfall protein, causing renal tubular congestion and damage [18]. Nitric oxide is consumed by plasma oxyhemoglobin, resulting in renal arteriole vasoconstriction and impaired kidney perfusion. Through the Fenton and Haber Weis processes, circulating labile iron enhances reactive oxygen species generation, exacerbating oxidative stress and acute kidney damage [19].

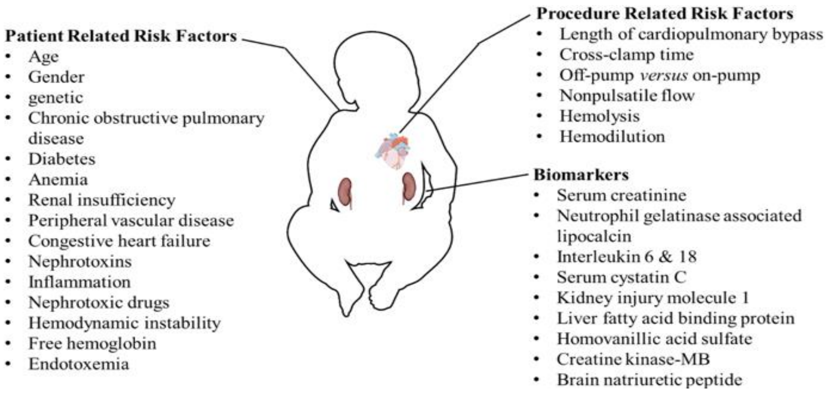

Figure 1. Risk factors & biomarkers associated with acute kidney injury after cardiac surgery in newborns (adapted from [14-16]).

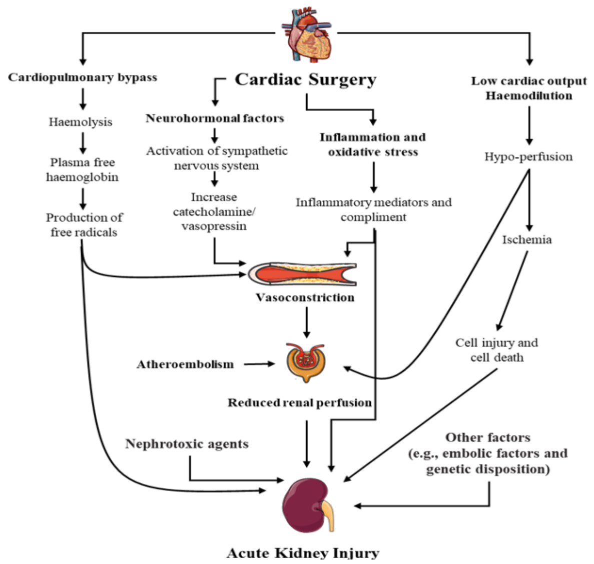

Figure 2. Pathogenesis of acute kidney injury after cardiac surgery in newborns (adapted from [17, 25, 26]).

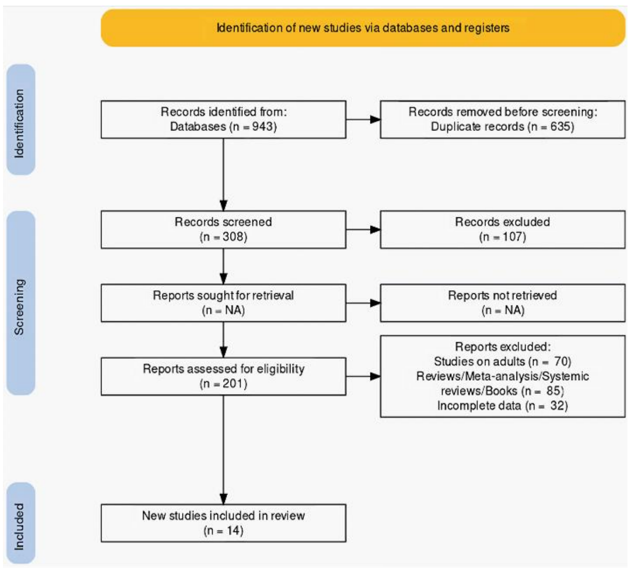

Figure 3. PRISMA flow chart of literature selection for meta-analysis (Source: Authors' own elaboration)

Renal damage is caused by cardiac surgery in a variety of ways. During cardiac bypass, low-pressure non-pulsatile linear flow causes an increase in peripheral vascular resistance and poor microcirculation, resulting in ischemia–perfusion damage and tissue edema [20, 21]. Furthermore, increased cortical perfusion, through increasing medullary oxygen demand, precipitates corticomedullary ischemia [22]. Low cardiac output also activates the sympathetic nervous system, leading in endogenous catecholamine release and stimulation of the renin-angiotensin-aldosterone cascade, further compromising renal oxygenation [23, 24]. The pathophysiology of acute renal damage associated with heart surgery is depicted in **Figure 2**.

Several methods have been tried in the pediatric population to lower the incidence of cardiac surgery-related acute renal damage, with varying degrees of effectiveness. The goal of this study is to see how effective different strategies are at preventing acute renal injury after juvenile heart surgery.

METHODS

In May 2022, we conducted a search of the PubMed and Medline databases for this meta-analysis, which included the most recent literature on randomized control trials and cohort studies for cardiac surgery-associated acute renal injury in neonates or children over the previous ten years. Medical subject headings thesaurus (MeSH) terms and keywords from relevant literature were used to build a search strategy that covers all relevant papers. The terms [Cardiac surgery] AND [acute renal injury] AND [newborns OR children OR neonates] AND [randomized control studies OR randomized control trials] were used as search criteria. We also looked through the reference tracking of bibliographies and manual searches during the first search to see if there were any additional studies that were relevant. The authors independently assessed the titles and abstracts for inclusion. The studies that met the inclusion criteria were considered qualified using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (**Figure 3**).

Following the removal of obvious unrelated material, the authors analyzed the study abstracts and complete texts independently, determining which papers to include based on the inclusion and exclusion criteria (**Table 1**). All writers discussed and resolved any concerns or conflicts.

Statistical Analysis

The retrieved data was examined with a 95% confidence interval using Review Manager 5.4. The random model was used to determine the heterogeneity among the studies. To determine the entire cumulative impact, forest patches were developed. We adopted a random effects model because we expected heterogeneity among publications in meta-analysis.

Table 1. Criteria for inclusion & exclusion of studies in meta-analysis

Inclusion	Exclusion
Original article	Reviews
Randomized control trials	Meta-analysis
Cardiac surgery	Systemic reviews
Acute kidney injury	Books/documents
Children/newborn/neonates	Studies not related to children/newborn/neonates

RESULTS

Following the initial search 943 articles were identified and 635 duplicate records were removed. The title and abstracts of the articles were reviewed, and 107 articles were excluded from the study. The remaining 201 articles were reviewed thoroughly, and further screening was done based on study. 14 articles found eligible and the articles having original studies related to treatment options were included in the study. All selected studies were from last 10 years and including 2,941 infants or children from those 931 developed acute kidney injury. The highest percentage of selected studies has been conducted in the USA (60%) followed by Finland and South Korea (13%). While 7% of studies have been conducted in Iran and Russia as presented in **Figure 4**.

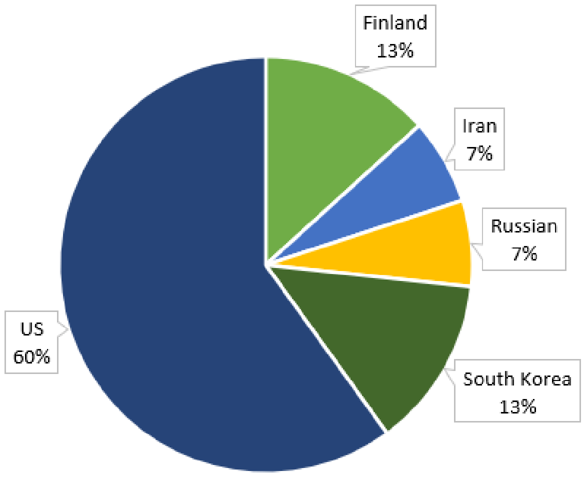

Figure 4. Country wise distribution of randomized controlled trial studies in cardiac surgery-associated acute kidney injury in newborns (Source: Authors' own elaboration)

The characteristics of the fourteen randomized controlled trials have been shown in **Table 2**. These studies included 2095 infants or children received treatments with steroids, aminophylline, dexmedetomidine and acetaminophen. While 846 infants or children were in control group in these studies.

Table 2. Characteristics of studies in cardiac surgery-associated acute kidney injury in pediatrics

Author	Country	Treatment (dose)	Age, mean±SD/ median (IQR)		Findings
			TG	CG	
[27]	South Korea	Dexmedetomidine (1 µg/kg)	NA	NA	Authors stated that their research will allow them to determine whether dexmedetomidine can affect early neurodevelopmental outcomes in newborns having heart surgery with cardiopulmonary bypass, as well as determine impact of dexmedetomidine on other organs.
[28]	Russian	Dexamethasone (1 mg/kg)	6.5 (4.0-9.3) months	5.7 (3.8-9.3) months	In comparison to placebo, intraoperative dexamethasone did not significantly reduce serious complications or mortality after 30 days.
[29]	USA	Methylprednisolone (30 mg/kg)	9.1 (5.4) days	8.2 (5.6) days	Intraoperative methylprednisolone failed to show a statistically meaningful reduction in composite primary study endpoint's occurrence.
[30]	Finland	Methylprednisolone (2 mg/kg) followed by hydrocortisone infusion (0.2 mg/kg/h)	8.1±2.6 days	8.2±4.7 days	A study found that corticosteroid administration lowered inflammatory response in neonates having heart surgery but did not diminish frequency of acute renal injury as characterized by kidney disease: decreasing growth of acute kidney injury biomarkers or improving global outcomes (KDIGO) classification.
[31]-PC	USA	Acetaminophen (60-70 mg/kg)	5.5 (3.3-16.6) months	15.2 (4.5-70.9) months	In pediatric patients undergoing heart surgery, early postoperative acetaminophen administration may be linked to a decreased likelihood of acute renal injury.
[31]-VC	USA	Acetaminophen (60-70 mg/kg)	6.7 (2.9-46.9) months	39.8 (5.3-203.9) months	
[32]	South Korea	Dexmedetomidine (0.5 mg/kg/hr)	31±14 months	32±19 months	Dexmedetomidine infusions given intraoperatively may lower risk of acute renal damage & delay decline in estimated glomerular filtration rates after bypass surgery.
[33]	USA	Dexmedetomidine (0.5 µg/kg/hr)	10 (4, 36) months	7 (3, 47) months	Use of a dexmedetomidine infusion in pediatric patients following congenital heart surgery was linked to a lower incidence of acute renal injury but not to changes in clinical outcomes.
[34]	USA	Steroid	NA	NA	Intraoperative steroids were widely used in major multi-center single ventricle reconstruction experiment. In neonates receiving norwood operation, intraoperative steroid treatment was not associated with improved outcomes & may be associated with a reduction in hospital survival.
[35]	Finland	Methylprednisolone (30 mg/kg)	9.9±7.0 days	11.0±7.2 days	Methylprednisolone, given before surgery, significantly lowers plasma neutrophil gelatinase–associated lipocalin levels. Neutrophil gelatinase–associated lipocalin appears to come from active neutrophils to a large extent. When interpreting plasma neutrophil gelatinase–associated lipocalin levels as a kidney damage marker in paediatric heart surgery, preoperative methylprednisolone can be a confusing factor.
[36]	US	Aminophylline (5 mg/kg)	154 (50-656) days	165 (58-1,333) days	Aminophylline had no effect on preventing acute renal injury in children recovering from heart surgery with cardiopulmonary bypass.

Table 2 (Continued). Characteristics of studies in cardiac surgery-associated acute kidney injury in pediatrics

Author	Country	Treatment (dose)	Age, mean±SD/ median (IQR)		Findings
			TG	CG	
[37]	USA	Aminophylline (5 mg/kg)	NA	NA	In early postoperative phase, intraoperative aminophylline was more efficient than furosemide in reversing oliguria. Children in aminophylline group had fewer acute kidney injuries that required renal replacement treatment.
[38]	Iran	Methylprednisolone (30 mg/kg)	39.8±24.7 months	38.2±19.8 months	After correcting tetralogy of fallot, a single dosage of methylprednisolone (corticosteroid) has no effect on clinical outcome.
[39]	USA	Hydrocortisone IV bolus (50 mg/m^2)	5 (4, 7) days	6 (5, 11) days	After neonatal cardiopulmonary bypass surgery, prophylactic postoperative hydrocortisone lowers low cardiac output syndrome, improves fluid balance & urine output, & minimizes inflammation.
[40]	USA	Acetaminophen (15 mg/kg)	33.1±9.2 months	34.1±8.9 months	Acetaminophen did not affect postoperative creatinine, urinary neutrophil gelatinase-associated lipocalin, or prevalence of acute kidney injury. Acetaminophen attenuated increase in plasma isoflurane concentrations.

Note. Reference for each study has been added; TG: Treatment group; CG: Control group; PC: Primary cohort; & VC: Validation cohort

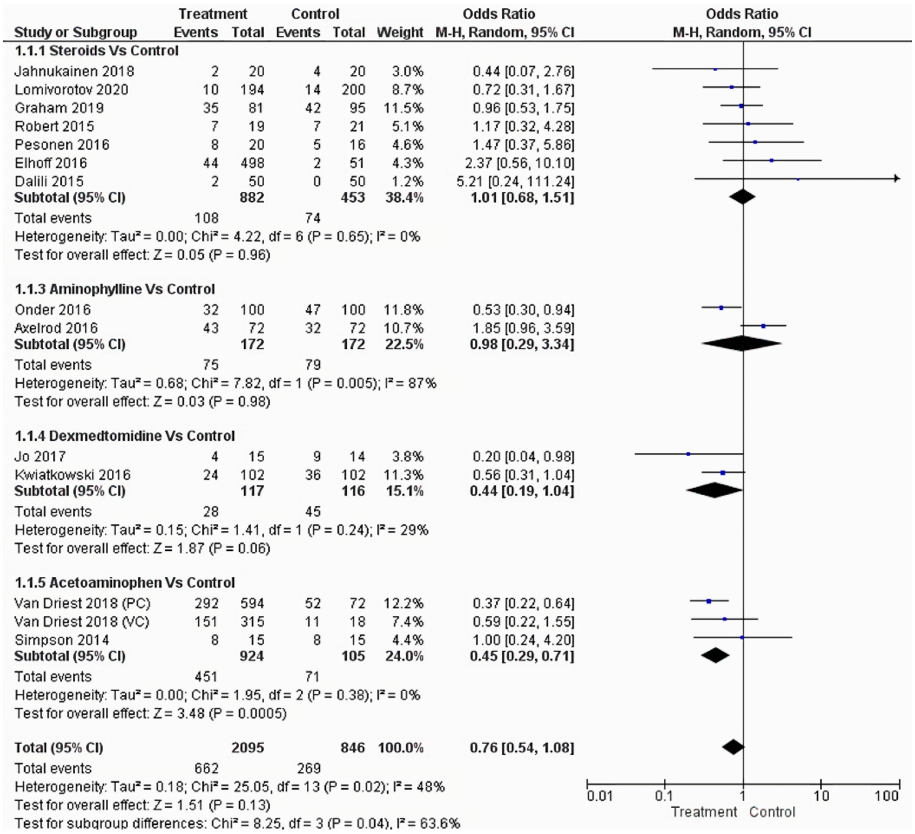

Figure 5. Forest plot of treatment & control groups with cardiac surgery-associated acute kidney injury in pediatrics (Source: Authors' own elaboration)

The results of the meta-analyses have been presented in **Figure 5**. Seven studies in the forest plot compared steroids treatment with control groups showed non-significant difference (p=0.6500) in heterogeneity among the groups with 0% I^2 value. The odds ratio (OR) for these studies showed no significant difference compared with control for steroids (OR, 1.01; 95% CI, 0.68 to 1.51; p=0.9600). Two studies compared aminophylline treatment groups with control groups, and there was a high degree of heterogeneity among the studies (I^2=87%, p=0.0050). The OR for these studies showed non-significant difference compared with control for aminophylline (OR, 0.98; 95% CI, 0.29, 3.34).

Similarly, other two studies compared dexmedetomidine treatment groups with control groups and there was a low heterogeneity among the studies (I^2=29%, p=0.2400). Whereas overall effect was non-significant (p=0.0600). The OR for these studies showed no significant difference compared with control for dexmedetomidine (OR, 0.44; 95% CI, 0.19, 1.04). The three studies compared acetaminophen treatment groups with control groups and there was a low heterogeneity among the studies (I^2=0%, p=0.3800).

The OR for these studies showed significant difference compared with control for acetaminophen (OR, 0.45; 95% CI, 0.29, 0.71). Whereas overall there was significant difference among acetaminophen treatment and control groups (p=0.0005). The combined effect of various treatments by using a random model was 0.76 (0.54, 1.08), the heterogeneity with I^2=48%. Overall, there was significant difference in treatment and control groups among all selected studies (p=0.0200) and subgroups (p=0.0400).

DISCUSSION

Following cardiac surgery in infants, acute kidney injury is common, followed by a rapid decline in kidney function as demonstrated by a lower glomerular filtration rate [1]. The goal of this meta-analysis was to compile the existing evidence and analyze the efficacy of pharmacological therapies in preventing cardiac surgery-related acute renal damage in children. A total of 2,941 newborns or children were enrolled in fourteen studies, with 931 developing acute renal damage. 2,095 of the enrolled infants and children received steroid, aminophylline, dexmedetomidine, and acetaminophen therapies. The USA (60%) has the largest percentage of selected studies, followed by Finland and South Korea (13%). In Iran and Russia, just 7% of studies have been conducted. Seven studies in the forest plot comparing steroids treatment to control groups revealed a non-significant difference (p=0.6500) in heterogeneity among the groups with a 0% I^2 score. The OR for steroids in these trials was not significantly different from control (OR, 1.01; 95% CI, 0.68 to 1.51; p=0.96). It was found that intraoperative dexamethasone did not significantly reduce serious complications or mortality at 30 days when compared to placebo [28]. Dexamethasone injection before cardiopulmonary bypass reduces the post-bypass inflammatory response in children, as measured by cytokine levels and clinical outcome [41]. Another study found that a single dosage of methylprednisolone (corticosteroid) has no effect on the clinical outcome after tetralogy of fallot repair [38]. Similarly, intraoperative methylprednisolone failed to show a meaningful reduction in the composite primary study endpoint's incidence. However, there was a benefit in patients undergoing palliative treatments, and there was a significant interaction between treatment effect and center, implying that there may be center or patient characteristics that make prophylactic methylprednisolone advantageous [29]. Another study found that corticosteroid administration lowered the inflammatory response in neonates having heart surgery but did not diminish the frequency of acute renal injury as characterized by kidney Disease: decreasing the growth of acute kidney injury biomarkers or improving global outcomes (KDIGO) classification [30]. Methylprednisolone, given before surgery, significantly lowers plasma neutrophil gelatinase–associated lipocalin levels. Neutrophil gelatinase–associated lipocalin appears to come from active neutrophils to a large extent. When interpreting plasma neutrophil gelatinase–associated lipocalin levels as a kidney damage marker in pediatric heart surgery, preoperative methylprednisolone can be a confusing factor [35]. After neonatal cardiopulmonary bypass surgery, prophylactic postoperative hydrocortisone lowers low cardiac output syndrome, improves fluid balance and urine output, and minimizes inflammation [39]. Intraoperative steroids were widely used in the major multi-center single ventricle reconstruction experiment. In neonates receiving the Norwood operation, intraoperative steroid treatment was not associated with improved outcomes and may be associated with a reduction in hospital survival [34].

In Two studies compared aminophylline treatment groups to control groups in this meta-analysis, and there was a lot of heterogeneity between them (I^2=87%, p=0.0050). The OR for aminophylline in these investigations was non-significant when compared to the control (OR, 0.98; 95% CI, 0.29, 3.34). According to [36] Aminophylline has no effect on preventing acute renal injury in children recovering from heart surgery with cardiopulmonary bypass. In the early postoperative phase, intraoperative aminophylline was more efficient than furosemide in reversing oliguria. Children in the aminophylline group had fewer acute kidney injuries that required renal replacement treatment [37].

Dexmedetomidine is a selective 2-agonist that is frequently used in perioperative anesthesia and analgesia. Recent evidence suggests that it can help safeguard renal function in adults who are having heart surgery [42], suggesting that it has nephroprotective qualities via reducing inflammation [43] and ischemia-reperfusion damage prevention [44]. The evidence for its role in pediatric patients is limited, with only two studies to date. In particular, a retrospective cohort study [33] first reported that dexmedetomidine was linked to a trend toward lower acute kidney injury incidence, albeit with marginal statistical significance; later, a randomized control trial [32] confirmed this effect and observed improved postoperative kidney function in children receiving dexmedetomidine. Two studies in this meta-analysis compared dexmedetomidine treatment groups to control groups, and there was little heterogeneity between them (I^2=29%, p=0.2400). The overall effect, however, was not significant (p=0.0600). The OR for dexmedetomidine in these investigations was not significantly different from the control (OR, 0.44; 95% CI, 0.19, 1.04). Dexmedetomidine infusions given intraoperatively may lower the risk of acute renal damage and delay the decline in estimated glomerular filtration rates after bypass surgery [32]. The use of a dexmedetomidine infusion in pediatric patients following congenital heart surgery was linked to a lower incidence of acute renal injury, but not to changes in clinical outcomes [33]. It was analyzed 2,625 pediatric participants from 14 research, including both randomized control trials and observational studies [45]. It was discovered that dexmedetomidine (OR: 0.49; 95% CI: 0.28 to 0.87) and acetaminophen (OR: 0.43; 95% CI: 0.28 to 0.67) significantly reduced acute renal injury, but corticosteroids, fenoldopam, and aminophylline had no effect. Dexmedetomidine was determined to be the best-ranking therapy in their assessments, despite overlap with the other therapies. The researchers in [27] planned to recruit 160 infants receiving cardiopulmonary bypass surgery with dexmedetomidine therapy. They stated that this research will allow them to determine whether dexmedetomidine can affect early neurodevelopmental outcomes in newborns having heart surgery with cardiopulmonary bypass, as well as estimate dexmedetomidine's effects on other organs.

Similarly, there is growing interest in the role of acetaminophen; while a randomized control trial in the field [40] found no significant benefit, a recent large-scale cohort [31] suggested that its perioperative administration could prevent acute kidney injury in a dose-dependent manner. However, because the study was retrospective, confounding could not be ruled out. Furthermore, prophylactic corticosteroid administration is a well-known technique for protecting children from relative adrenal insufficiency and a systemic inflammatory response generated by a cardiac bypass circuit [46]. Despite this, there is no evidence that its administration reduces the risk of acute kidney injury. Three studies were chosen to compare acetaminophen treatment groups with control groups in the current analysis, and there was little heterogeneity across them (I^2=0%, p=0.3800). The OR for acetaminophen in these investigations was significantly different from the control (OR, 0.45; 95% CI, 0.29, 0.71).

Overall, there was a significant difference (p=0.0005) between the acetaminophen treatment and control groups. Postoperative creatinine, urinary neutrophil gelatinase-associated lipocalin, or the prevalence of acute renal damage were not affected by acetaminophen. The increase in plasma isoflurane concentrations was reduced by acetaminophen [40]. In pediatric patients undergoing heart surgery, early postoperative acetaminophen administration may be linked to a decreased likelihood of acute kidney injury [31]. The overall effect of multiple treatments employing a random model in this meta-analysis was 0.76 (0.54, 1.08), with I^2=48% heterogeneity. All chosen studies (p=0.0200) and subgroups (p=0.0400) had significant differences in treatment and control groups.

CONCLUSION

14 articles found eligible and the articles having original studies related to treatment options were included in the study. The highest percentage of selected studies has been conducted in the USA (60%) followed by Finland and South Korea (13%). While 7% of studies have been conducted in Iran and Russia. The OR for these studies showed no significant difference compared with control for steroids (OR, 1.01; 95% CI, 0.68 to 1.51; p=0.9600). The OR for these studies showed no significant difference compared with control for dexmedetomidine (OR, 0.44; 95% CI, 0.19, 1.04). The finding of this meta-analyses also suggested that acetaminophen was associated with lower incidence of postoperative acute kidney injury, while no benefit from steroids, and aminophylline administration could be supported. Future, more randomized controlled trials should be conducted to clarify the effectiveness of these drugs for protecting acute kidney injury in newborn.

Author contributions: All authors have sufficiently contributed to the study and agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Ethical statement: Authors stated that an ethics committee approval was not applicable because this study is based exclusively on published literature.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. Mao H, Katz N, Ariyanon W, et al. Cardiac surgery-associated acute kidney injury. Cardiorenal Med. 2013;3(3):178-99. https://doi.org/10.1159/000353134 PMid:24454314 PMCid:PMC3884176
2. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71(10):1028-35. https://doi.org/10.1038/sj.ki.5002231 PMid:17396113
3. Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31. https://doi.org/10.1186/cc5713 PMid:17331245 PMCid:PMC2206446
4. Tóth R, Breuer T, Cserép Z, et al. Acute kidney injury is associated with higher morbidity and resource utilization in pediatric patients undergoing heart surgery. Ann Thorac Surg. 2012;93(6):1984-90. https://doi.org/10.1016/j.athoracsur.2011.10.046 PMid:22226235
5. Li S, Krawczeski CD, Zappitelli M, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery–a prospective multicenter study. Crit Care Med. 2011;39(6):1493-9. https://doi.org/10.1097/CCM.0b013e31821201d3 PMid:21336114 PMCid:PMC3286600
6. Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. Crit Care Med. 2010;38(3):933-9. https://doi.org/10.1097/CCM.0b013e3181cd12e1 PMid:20124891
7. Blinder JJ, Goldstein SL, Lee V-V, et al. Congenital heart surgery in infants: Effects of acute kidney injury on outcomes. J Thorac Cardiovasc Surg. 2012;143(2):368-74. https://doi.org/10.1016/j.jtcvs.2011.06.021 PMid:21798562
8. Sethi SK, Kumar M, Sharma R, Bazaz S, Kher V. Acute kidney injury in children after cardiopulmonary bypass: Risk factors and outcome. Indian Pediatr. 2015;52(3):223-6. https://doi.org/10.1007/s13312-015-0611-4 PMid:25848999
9. Piggott KD, Soni M, Decampli WM, et al. Acute kidney injury and fluid overload in neonates following surgery for congenital heart disease. World J Pediatr Congenit Heart Surg. 2015;6(3):401-6. https://doi.org/10.1177/2150135115586814 PMid:26180155
10. Zappitelli M, Greenberg JH, Coca SG, et al. Association of definition of acute kidney injury by cystatin C rise with biomarkers and clinical outcomes in children undergoing cardiac surgery. JAMA Pediatr. 2015;169(6):583-91. https://doi.org/10.1001/jamapediatrics.2015.54 PMid:25844892 PMCid:PMC4506750
11. Hobson CE, Yavas S, Segal MS, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation. 2009;119(18):2444-53. https://doi.org/10.1161/CIRCULATIONAHA.108.800011 PMid:19398670
12. Lee E-H, Choi J-H, Joung K-W, et al. Relationship between serum uric acid concentration and acute kidney injury after coronary artery bypass surgery. J Korean Med Sci. 2015;30(10):1509-16. https://doi.org/10.3346/jkms.2015.30.10.1509 PMid:26425051 PMCid:PMC4575943
13. Basu RK, Wong HR, Krawczeski CD, et al. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. J Am Coll Cardiol. 2014;64(25):2753-62. https://doi.org/10.1016/j.jacc.2014.09.066 PMid:25541128 PMCid:PMC4310455
14. Singh SP. Acute kidney injury after pediatric cardiac surgery. Ann Card Anaesth. 2016;19(2):306-13. https://doi.org/10.4103/0971-9784.179635 PMid:27052074 PMCid:PMC4900346
15. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol. 2006;1(1):19-32. https://doi.org/10.2215/CJN.00240605 PMid:17699187
16. Wu B, Chen J, Yang Y. Biomarkers of acute kidney injury after cardiac surgery: A narrative review. Biomed Res Int. 2019;2019:7298635. https://doi.org/10.1155/2019/7298635 PMid:31346523 PMCid:PMC6620851

17. O'Neal JB, Shaw AD, Billings 4th FT. Acute kidney injury following cardiac surgery: Current understanding and future directions. Crit Care. 2016;20(1):187. https://doi.org/10.1186/s13054-016-1352-z PMid:27373799 PMCid:PMC4931708
18. Mamikonian LS, Mamo LB, Smith PB, Koo J, Lodge AJ, Turi JL. Cardiopulmonary bypass is associated with hemolysis and acute kidney injury in neonates, infants and children. Pediatr Crit Care Med. 2014;15(3):e111-9. https://doi.org/10.1097/PCC.0000000000000047 PMid:24394997 PMCid:PMC3951557
19. Haase M, Bellomo R, Haase-Fielitz A. Novel biomarkers, oxidative stress, and the role of labile iron toxicity in cardiopulmonary bypass-associated acute kidney injury. J Am Coll Cardiol. 2010;55(19):2024-33. https://doi.org/10.1016/j.jacc.2009.12.046 PMid:20447525
20. Ji B, Undar A. Comparison of perfusion modes on microcirculation during acute and chronic cardiac support: Is there a difference? Perfusion. 2007;22(2):115-9. https://doi.org/10.1177/0267659107080115 PMid:17708160
21. Hwang YJ, Hyun MC, Choi BS, Chun SY, Cho MH. Acute kidney injury after using contrast during cardiac catheterization in children with heart disease. J Korean Med Sci. 2014;29(8):1102-7. https://doi.org/10.3346/jkms.2014.29.8.1102 PMid:25120320 PMCid:PMC4129202
22. Ricksten S-E, Bragadottir G, Redfors B. Renal oxygenation in clinical acute kidney injury. Crit Care. 2013:17(2):221. https://doi.org/10.1186/cc12530 PMid:23514538 PMCid:PMC3672481
23. Fleming GA, Billings 4th FT, Klein TM, Bichell DP, Christian KG, Pretorius M. Angiotensin-converting enzyme inhibition alters the inflammatory and fibrinolytic response to cardiopulmonary bypass in children. Pediatr Crit Care Med. 2011;12(5):532-8. https://doi.org/10.1097/PCC.0b013e3181fe3925 PMid:20975611 PMCid:PMC3690292
24. Fujii T, Kurata H, Takaoka M, et al. The role of renal sympathetic nervous system in the pathogenesis of ischemic acute renal failure. Eur J Pharmacol. 2003;481(2-3):241-8. https://doi.org/10.1016/j.ejphar.2003.09.036 PMid:14642792
25. Harky A, Joshi M, Gupta S, Teoh WY, Gatta F, Snosi M. Acute kidney injury associated with cardiac surgery: A comprehensive literature review. Braz J Cardiovasc Surg. 2020;35(2):211-24. https://doi.org/10.21470/1678-9741-2019-0122 PMid:32369303 PMCid:PMC7199993
26. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: Risk factors, pathophysiology and treatment. Nat Rev Nephrol. 2017;13(11):697-711. https://doi.org/10.1038/nrneph.2017.119 PMid:28869251
27. Ji S-H, Kang P, Song I-S, et al. The effect of dexmedetomidine on neuroprotection in pediatric cardiac surgery patients: Study protocol for a prospective randomized controlled trial. Trials. 2022;23(1):271. https://doi.org/10.1186/s13063-022-06217-9 PMid:35395776 PMCid:PMC8991922
28. Lomivorotov V, Kornilov I, Boboshko V, et al. Effect of intraoperative dexamethasone on major complications and mortality among infants undergoing cardiac surgery: The DECISION randomized clinical trial. JAMA. 2020;323(24):2485-92. https://doi.org/10.1001/jama.2020.8133 PMid:32573670 PMCid:PMC7312411
29. Graham EM, Martin RH, Buckley JR, et al. Corticosteroid therapy in neonates undergoing cardiopulmonary bypass: Randomized controlled trial. J Am Coll Cardiol. 2019;74(5):659-68. https://doi.org/10.1016/j.jacc.2019.05.060 PMid:31370958 PMCid:PMC6684326
30. Jahnukainen T, Keski-Nisula J, Tainio J, et al. Efficacy of corticosteroids in prevention of acute kidney injury in neonates undergoing cardiac surgery—A randomized controlled trial. Acta Anaesthesiol Scand. 2018;62(8):1072-9. https://doi.org/10.1111/aas.13134 PMid:29667173
31. Van Driest SL, Jooste EH, Shi Y, et al. Association between early postoperative acetaminophen exposure and acute kidney injury in pediatric patients undergoing cardiac surgery. JAMA Pediatr. 2018;172(7):655-63. https://doi.org/10.1001/jamapediatrics.2018.0614 PMid:29799947 PMCid:PMC6110290
32. Jo YY, Kim JY, Lee JY, Choi CH, Chang YJ, Kwak HJ. The effect of intraoperative dexmedetomidine on acute kidney injury after pediatric congenital heart surgery: A prospective randomized trial. Medicine (Baltimore). 2017;96(28):e7480. https://doi.org/10.1097/MD.0000000000007480 PMid:28700489 PMCid:PMC5515761
33. Kwiatkowski DM, Axelrod DM, Sutherland SM, Tesoro TM, Krawczeski CD. Dexmedetomidine is associated with lower incidence of acute kidney injury after congenital heart surgery. Pediatr Crit Care Med. 2016;17(2):128-34. https://doi.org/10.1097/PCC.0000000000000611 PMid:26673841
34. Elhoff JJ, Chowdhury SM, Zyblewski SC, Atz AM, Bradley SM, Graham EM. Intraoperative steroid use and outcomes following the norwood procedure: An analysis of the pediatric heart network's public database. Pediatr Crit Care Med. 2016;17(1):30-5. https://doi.org/10.1097/PCC.0000000000000541 PMid:26492058 PMCid:PMC4703451
35. Pesonen EJ, Suominen PK, Keski-Nisula J, Mattila IP, Rautiainen P, Jahnukainen T. The effect of methylprednisolone on plasma concentrations of neutrophil gelatinase–associated lipocalin in pediatric heart surgery. Pediatr Crit Care Med. 2016;17(2):121-7. https://doi.org/10.1097/PCC.0000000000000573 PMid:26509817
36. Axelrod DM, Sutherland SM, Anglemyer A, Grimm PC, Roth SJ. A double-blinded, randomized, placebo-controlled clinical trial of aminophylline to prevent acute kidney injury in children following congenital heart surgery with cardiopulmonary bypass. Pediatr Crit Care Med. 2016;17(2):135-43. https://doi.org/10.1097/PCC.0000000000000612 PMid:26669642 PMCid:PMC4740222
37. Onder AM, Rosen D, Mullett C, et al. Comparison of intraoperative aminophylline versus furosemide in treatment of oliguria during pediatric cardiac surgery. Pediatr Crit Care Med. 2016;17(8):753-63. https://doi.org/10.1097/PCC.0000000000000834 PMid:27355823 PMCid:PMC5515381
38. Dalili M, Vesal A, Tabib A, Khani-Tafti L, Hosseini S, Totonchi Z. Single dose corticosteroid therapy after surgical repair of Fallot's tetralogy; a randomized controlled clinical trial. Res Cardiovasc Med. 2015;4(1):e25500. https://doi.org/10.5812/cardiovascmed.25500 PMid:25789260 PMCid:PMC4350157

39. Robert SM, Borasino S, Dabal RJ, Cleveland DC, Hock KM, Alten JA. Postoperative hydrocortisone infusion reduces the prevalence of low cardiac output syndrome after neonatal cardiopulmonary bypass. Pediatr Crit Care Med. 2015;16(7):629-36. https://doi.org/10.1097/PCC.0000000000000426 PMid:25901540
40. Simpson SA, Zaccagni H, Bichell DP, et al. Acetaminophen attenuates lipid peroxidation in children undergoing cardiopulmonary bypass. Pediatr Crit Care Med. 2014;15(6):503-10. https://doi.org/10.1097/PCC.0000000000000149 PMid:24732290 PMCid:PMC4087071
41. Bronicki RA, Backer CL, Baden HP, Mavroudis C, Crawford SE, Green TP. Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg. 2000;69(5):1490-5. https://doi.org/10.1016/S0003-4975(00)01082-1 PMid:10881828
42. Liu Y, Sheng B, Wang S, Lu F, Zhen J, Chen W. Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: A meta-analysis of randomized controlled trials. BMC Anesthesiol. 2018;18(1):7. https://doi.org/10.1186/s12871-018-0472-1 PMid:29334927 PMCid:PMC5769334
43. Tan F, Chen Y, Yuan D, Gong C, Li X, Zhou S. Dexmedetomidine protects against acute kidney injury through downregulating inflammatory reactions in endotoxemia rats. Biomed Rep. 2015;3(3):365-70. https://doi.org/10.3892/br.2015.427 PMid:26137237 PMCid:PMC4467244
44. Gu J, Sun P, Zhao H, et al. Dexmedetomidine provides renoprotection against ischemia-reperfusion injury in mice. Crit Care. 2011;15(3):R153. https://doi.org/10.1186/cc10283 PMid:21702944 PMCid:PMC3219027
45. Bellos I, Iliopoulos DC, Perrea DN. Pharmacological interventions for the prevention of acute kidney injury after pediatric cardiac surgery: A network meta-analysis. Clin Exp Nephrol. 2019;23(6):782-91. https://doi.org/10.1007/s10157-019-01706-9 PMid:30734166
46. Fudulu DP, Gibbison B, Upton T, et al. Corticosteroids in pediatric heart surgery: Myth or reality. Front Pediatr. 2018;6:112. https://doi.org/10.3389/fped.2018.00112 PMid:29732365 PMCid:PMC5920028