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REVIEW ARTICLE

WILEY Congenital Heart Disease

Hemodynamic effects of ketamine in children with congenital heart disease and/or pulmonary hypertension

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Abstract

Introduction: Ketamine is a drug often used for procedural sedation or as adjunct agent for general sedation in children with congenital heart disease. In the clinical realm, there is often confusion regarding the effects of ketamine on hemodynamics, particularly pulmonary vascular resistance and systemic vascular resistance. We performed a meta-analysis of studies investigating the effects of ketamine on hemodynamics.

Methods: A systematic review was conducted to identify studies characterizing the hemodynamic effects of ketamine in children with congenital heart disease. Studies were assessed for quality and those of satisfactory quality with pre- and postketamine hemodynamics for each patient were included in the final analyses. Those not limited to pediatric patients and those not limited to patients with congenital heart disease were excluded from the final analyses.

Results: A total of 7 studies with 139 patients were included in the final analyses. Pulmonary vascular resistance, systemic vascular resistance, mean pulmonary artery pressure, mean systemic pressure, heart rate, pH, and arterial oxygen concentration did not significantly change with administration of ketamine. Carbon dioxide concentration did increase significantly by a mean of 1.38 mm Hg with the administration of ketamine.

Conclusion: Ketamine has minimal impact on hemodynamics in children with congenital heart disease when used at usual clinical doses. Systemic vascular resistance and pulmonary vascular resistance are not significantly altered. Blood gas values are also only minimally affected by ketamine.

KEYWORDS

congenital heart disease, hemodynamics, ketamine, systemic vascular resistance

1 | INTRODUCTION

Ketamine is a chemical derivative of phencyclidine acting as a selective antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor that participates in analgesia, amnesia, and sedation pathways.[1] Besides NMDA receptor antagonism, other known actions of ketamine include: partial agonist of the dopamine D2 receptor,[2] muscarinic acetylcholine receptor antagonist[3] and inhibitor of cholinesterase.[4] In addition, ketamine produces cardiovascular stimulation and appears to be mediated by central activation of the sympathetic nervous system associated with increased plasma levels of epinephrine and norepinephrine.[5] The sympathetic activation with support of the blood pressure and heart rate and maintenance of airway reflexes and respiratory drive, has made ketamine a frequently used agent for induction of anesthesia in children with congenital heart disease and/or pulmonary hypertension.[6]

Ketamine has been implicated in modifications of the systemic or pulmonary artery pressure and pulmonary or systemic vascular resistance.[7,8] However, other studies have demonstrated conflicting results with no significant changes in pulmonary artery pressure, pulmonary or systemic vascular resistance after a dose of ketamine in children with atrial or ventricular septal defects, atrioventricular canal defects, or tetralogy of Fallot.[9,10] Hence, there is often confusion regarding the effects of ketamine on hemodynamics in this patient population. We, therefore, performed a meta-analysis of studies investigating the effects of ketamine on hemodynamics.

2 | METHODS

As this study is a systemativ review of previously published literature and uses no identifiable patient data from a specific institution, approval from the institutional review board was not needed.

2.1 | End points

A systematic review of the literature was performed to identify manuscripts describing hemodynamics in children with congenital heart disease and/or pulmonary hypertension before and after administration of ketamine. This was a newly conducted review with no previous review protocol having been established. A meta-analysis was conducted to determine the hemodynamic effects of ketamine in children with congenital heart disease with attention to the following outcomes: systemic vascular resistance, pulmonary vascular resistance, mean pulmonary artery pressure, mean systemic pressure, heart rate, pH, blood oxygen concentration, and blood carbon dioxide concentration. Systemic vascular resistance and pulmonary vascular resistance are presented in Wood units/m^2 (wu/m^2). Mean pulmonary artery pressure and mean systemic pressure are presented in millimeters of mercury (mm Hg). Heart rate is presented in beats per minute (bpm). Blood oxygen concentration and blood carbon dioxide concentration are presented in mm Hg.

2.2 | Manuscript search and identification strategy

Published manuscripts were identified by searching PubMed and EMBASE. The following search terms were used to query the databases: "ketamine," "congenital heart disease," "hemodynamics," "systemic vascular resistance," "pulmonary vascular resistance," "pulmonary artery pressure," "blood pressure," "pulmonary hypertension." No specific restriction on the year of publication was used. Manuscripts were initially screened by title and abstract with full text being retrieved for select manuscripts.

These full text manuscripts were then reviewed by the authors and assess for quality and bias. Any disparities in scoring was discussed. The Cochrane Handbook for Systematic Review was used for quality evaluation. Criteria for inclusion consisted of studies published in English characterizing hemodynamics before and after ketamine. For inclusion, a study must have included pre- and postketamine data for at least one of the end points of interest, include only patients under 18 years of age, and include only patients with congenital heart disease. Data for the end points had to include number of patients, mean or median pre- and postketamine values, as well as a *P* value for the association. Studies not meeting these criteria were excluded. Additionally, studies in which the postketamine hemodynamics were assess less than 2 minutes or greater than 5 minutes from ketamine administration were also excluded.

2.3 | Data extraction

Data regarding baseline patient characteristics and identified outcomes were extracted from the manuscripts identified for inclusion. Trial level data was extracted using a data collection form. The extracted data were double checked to ensure the integrity of the extracted data. If no information was available for a particular outcome this was also recorded. Authors of included studies were not contacted for additional data.

2.4 | Bias analysis

Bias analysis was performed with specific attention paid to patient selection, intervention selection, end point inclusion, and result reporting of identified studies.

2.5 | Data analysis

Meta-analyses were characterized using Comprehensive Meta-Analysis Version 3.0 (Biostat, Englewood, New Jersey). A fixed-effects model was run initially for each end point. Heterogeneity was assessed using the *Q*-statistic and its result *P* value as well as the I^2 value. A significant *Q*-statistic (*P* value of less than .05) or an I^2 of greater than 50% was considered to represent significant heterogeneity and prompted the use of a random effects model for that end point. As all end points are continuous variables the results are presented as mean differences with 95% confidence intervals. Results are represented graphically by use of forest plots.

For studies in which patient data were presented for separate groups of patients, each group of patients was treated as a separate study in the meta-analyses. This is represented in the forest plots. In the text, the number of studies is presented as the true number of studies pooled, irrespective of the number of groups. Next, publication bias was assessed qualitatively by the use of funnel plots and quantitatively by means of the Egger analysis. An Egger analysis with a *P* value of less than .05 was once again considered to be significant. These analyses were conducted separately for each end point.

Finally, a meta-regression was conducted for each end point. The following data points were used in the meta-regression: study year, ketamine dose in mg/kg, time from administration to postketamine hemodynamic measurement (minutes), gender (percent of study

population that are male), mean patient age (years), and whether the study was conducted in the catheterization laboratory.

3 | RESULTS

3.1 | Manuscript identification and characteristics

A total of 236 manuscripts were identified with 93 remaining after removal of duplicates. Abstracts for these 93 manuscripts were reviewed and a total of 42 had their full-text reviewed after elimination of animal studies, review articles, non-English studies, and studies not pertaining to the question of our review. A total of 7 studies with 139 patients were identified for inclusion in the meta-analyses (Figure 1).[9–15] Pre- and postketamine hemodynamic data were available for the 139 patients included in the final review. Only study level data were available and no patient level data were available.

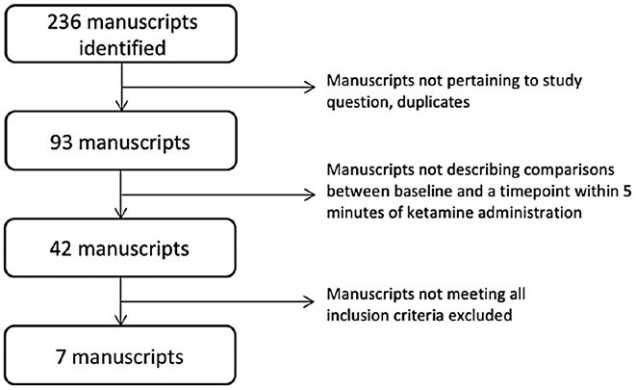

FIGURE 1 Flowchart demonstrating study selection

Average age of the patients in the included studies was 5.8 years. The average dose of ketamine administered in these studies was 3.3 mg/kg. The lowest dose used was 1 mg/kg while the highest was 10 mg/kg. A majority of studies used 2 mg/kg as the ketamine dose. Average time from ketamine administration to postketamine hemodynamic assessment was 3.5 minutes with a range of 2-5 minutes.

Of the seven studies, five were done in the catheterization laboratory, one was done in the intensive care unit by use of surgically placed lines that were being transduced, and one was done in the operating room immediately preceding cardiac surgery.

3.2 | Bias analysis

Included studies were found to have low overall levels of bias.

3.3 | Systemic vascular resistance

All seven studies presented data regarding systemic vascular resistance.[9-15] These provided data from 139 patients. The *P* value for the *Q* statistic was <.001 and the I^2-statistic was 78%, demonstrating significant heterogeneity. Due to the heterogeneity, a random effects model was used to pool these data. An Egger's regression was conducted and resulted in a *P* value of less than .05 demonstrating significant publication bias.

There was no statistically significant difference in systemic vascular resistance with the administration of ketamine. The mean difference in systemic vascular resistance was found to be .04 wu/m^2 (95% confidence interval −1.15 to 1.23, *P* = .944) (Figure 2).

Meta-regression demonstrated the following statistically significant associations: greater increase in systemic vascular resistance with increasing age, greater decrease in systemic vascular resistance with increasing time from ketamine administration. The following

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Wolfe et al (Group 1)	1.000	2.598	6.750	-4.092	6.092	0.385	0.700
Wolfe et al (Group 2)	1.400	2.160	4.667	-2.834	5.634	0.648	0.517
Wolfe et al (Group 3)	0.900	1.803	3.250	-2.633	4.433	0.499	0.618
Williams et al	-0.900	1.499	2.246	-3.837	2.037	-0.601	0.548
Oklu et al (Group 1)	-2.900	2.532	6.413	-7.863	2.063	-1.145	0.252
Oklu et al (Group 2)	7.400	1.838	3.378	3.798	11.002	4.027	0.000
Oklu et al (Group 3)	3.760	1.820	3.312	0.193	7.327	2.066	0.039
Morray et al	-0.750	0.949	0.900	-2.609	1.109	-0.791	0.429
Hickey et al (Group 1)	-2.000	0.378	0.143	-2.741	-1.259	-5.292	0.000
Hickey et al (Group 2)	-2.000	0.378	0.143	-2.741	-1.259	-5.292	0.000
Han et al	-1.300	0.720	0.519	-2.711	0.111	-1.805	0.071
Friesen et al	1.390	0.989	0.979	-0.549	3.329	1.405	0.160
	0.043	0.609	0.371	-1.152	1.237	0.070	0.944

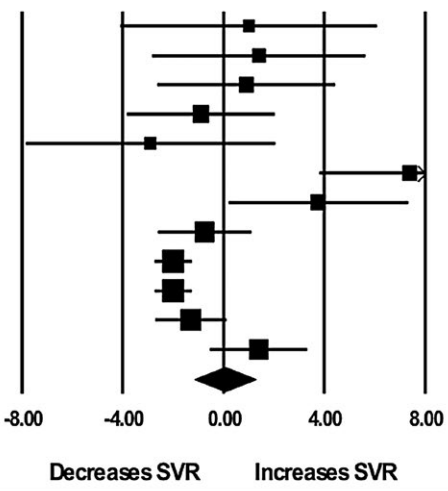

FIGURE 2 Forest plot demonstrating the individual and pooled results for effect of ketamine on systemic vascular resistance (SVR)

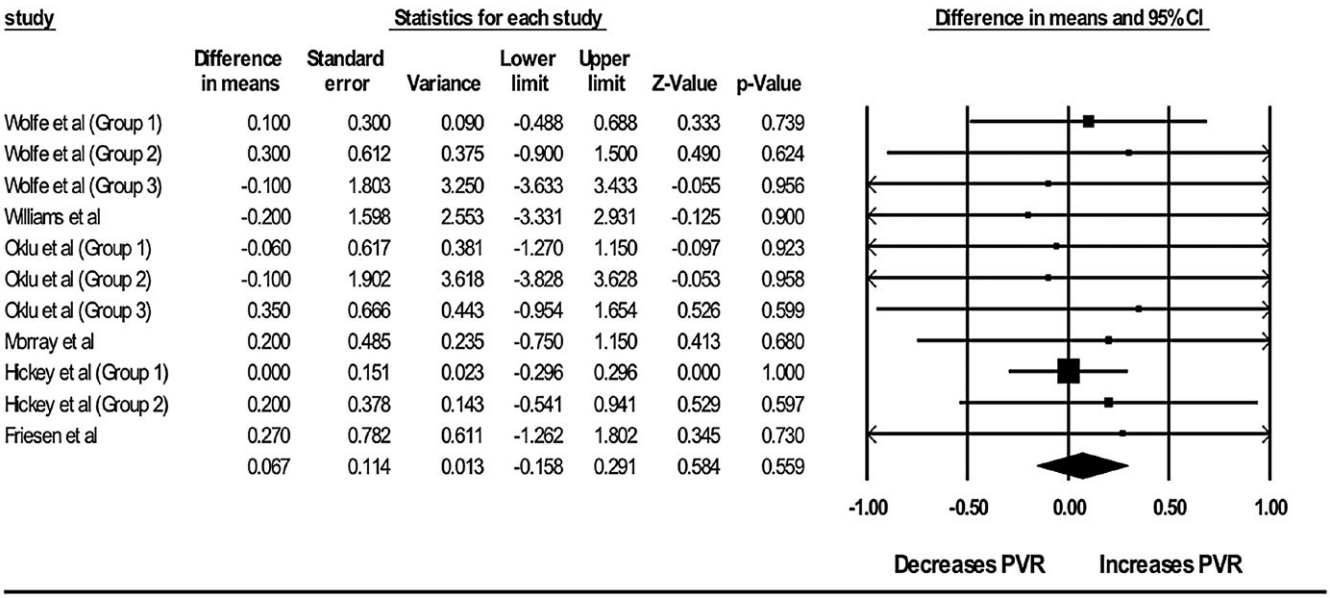

FIGURE 3 Forest plot demonstrating the individual and pooled results for effect of ketamine on pulmonary vascular resistance (PVR)

were noted not to be significantly associated with change in systemic vascular resistance: ketamine dose and gender.

3.4 | Pulmonary vascular resistance

A total of six studies presented data regarding pulmonary vascular resistance.[9–14] These provided data from 117 patients. The *P* value for the *Q* statistic was 1.000 and so a fixed-effects model was used to pool these data. An Egger's regression was conducted and resulted in a *P* value of .212 demonstrating no significant publication bias.

There was no statistically significant difference in pulmonary vascular resistance with the administration of ketamine. The mean difference was found to be 0.06 wu/m^2 (95% confidence interval −0.15 to 0.20, *P* = .559) (Figure 3).

Meta-regression demonstrated that age, time from ketamine administration, ketamine dose, and gender did not significantly impact the change in pulmonary vascular resistance after ketamine administration.

3.5 | Mean systemic arterial pressure

A total of five studies presented data regarding mean systemic arterial pressure.[9,10,12,13,15] These provided data from 111 patients. The *P* value for the *Q* statistic was <.001 and so a random effects model was used to pool these data. An Egger's regression was conducted and resulted in a *P* value of .969 demonstrating no significant publication bias.

There was no statistically significant difference in the mean systemic arterial pressure with the administration of ketamine. The mean difference was found to be 1.80 mm Hg (95% confidence interval −6.28 to 9.88, *P* = .662) (Figure 4).

Meta-regression demonstrated the following statistically significant associations: greater increase in mean systemic arterial pressure with increasing age, greater decrease in mean systemic arterial pressure with increasing ketamine dose, and greater decrease in systemic arterial pressure in males. Time from ketamine administration did not have a significant impact on the change in mean systemic arterial pressure after ketamine administration.

3.6 | Cardiac index

A total of five studies presented data regarding cardiac index.[9,11,13–15] These provided data from 104 patients. The *P* value for the *Q* statistic was .001 and the I^2-statistic was 78% so a random effects model was used to pool these data. An Egger's regression was conducted and resulted in a *P* value of .357 demonstrating no significant publication bias.

There was no statistically significant difference in cardiac index with the administration of ketamine. The mean difference 0.02 l/min/m^2 (95% confidence interval −0.35 to 0.39, *P* = .904) (Figure 5).

Meta-regression demonstrated the following statistically significant associations: greater increase in cardiac index with increasing age and greater decrease in cardiac index with increasing ketamine dose. Time from ketamine dose and gender did not have a significant impact on the change in cardiac index after ketamine administration.

3.7 | Heart rate

A total of six studies presented data regarding heart rate.[9,10,12–15] These provided data from 125 patients. The *P* value for the *Q* statistic was .003 and so a random effects model was used to pool these data. An Egger's regression was conducted and resulted in a *P* value of .928 demonstrating no significant publication bias.

There was no statistically significant difference in heart rate with the administration of ketamine. The mean difference was found to

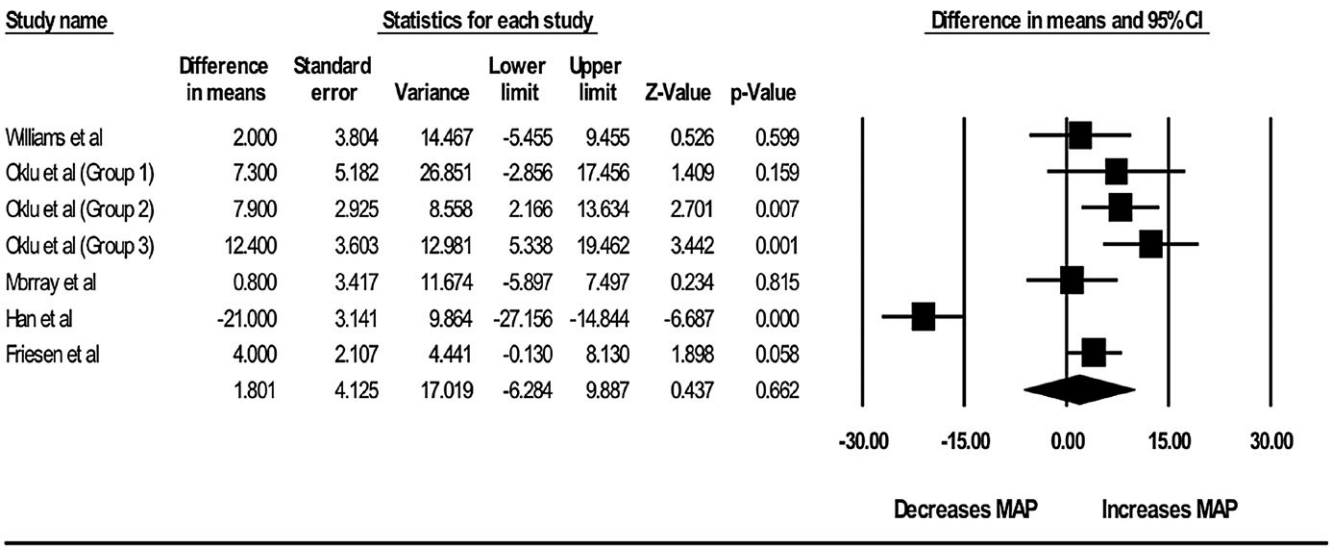

FIGURE 4 Forest plot demonstrating the individual and pooled results for effect of ketamine on mean systemic arterial pressure (MAP)

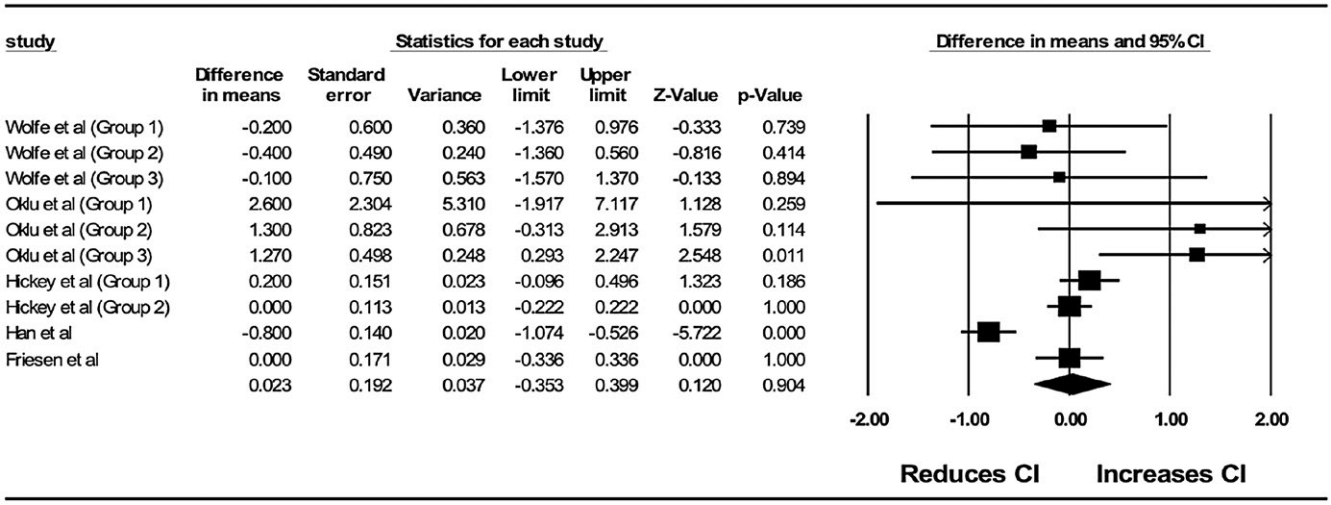

FIGURE 5 Forest plot demonstrating the individual and pooled results for effect of ketamine on cardiac index

be −0.95 bpm (95% confidence interval −5.75 to 3.84, $P = .697$) (Figure 6).

Meta-regression demonstrated the following statistically significant associations: greater decrease in heart rate with increasing ketamine dose, and greater decrease in heart rate in males. There was no significant impact of age or time from ketamine administration on the change in heart rate.

3.8 | pH

A total of five studies presented data regarding pH.[9,11–14] These provided data from 97 patients. The *P* value for the *Q* statistic was .787 and so a fixed-effects model was used to pool these data. An Egger's regression was conducted and resulted in a *P* value of .923 demonstrating no significant publication bias.

There was no statistically significant difference in pH with the administration of ketamine. The mean difference was −0.01 (95% confidence interval −0.01 to 0.00, $P = .057$) (Figure 7).

Meta-regression demonstrated that age, time from ketamine administration, ketamine dose, and gender did not significantly impact the change in pulmonary vascular resistance after ketamine administration.

3.9 | Blood carbon dioxide concentration

A total of six studies presented data regarding blood carbon dioxide concentration.[9–14] These provided data from 117 patients. The *P* value for the *Q* statistic was .008 and the I^2-statistic was 57% so a random effects model was used to pool these data. An Egger's regression was conducted and resulted in a *P* value of .123 demonstrating no significant publication bias.

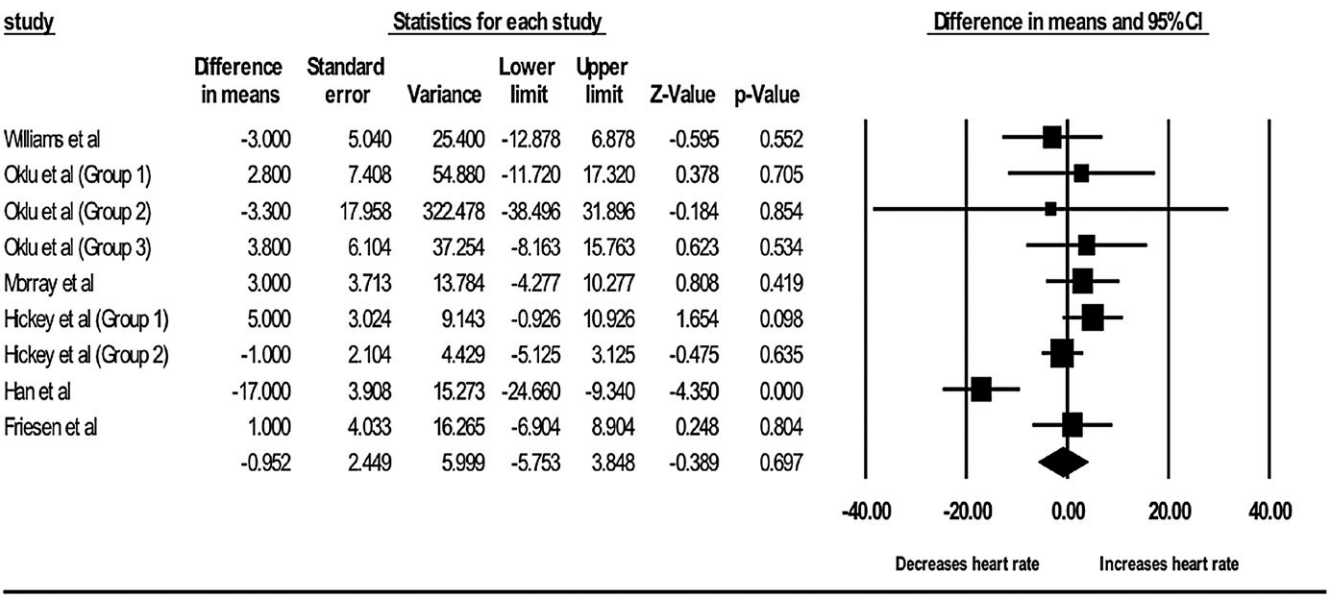

FIGURE 6 Forest plot demonstrating the individual and pooled results for effect of ketamine on heart rate

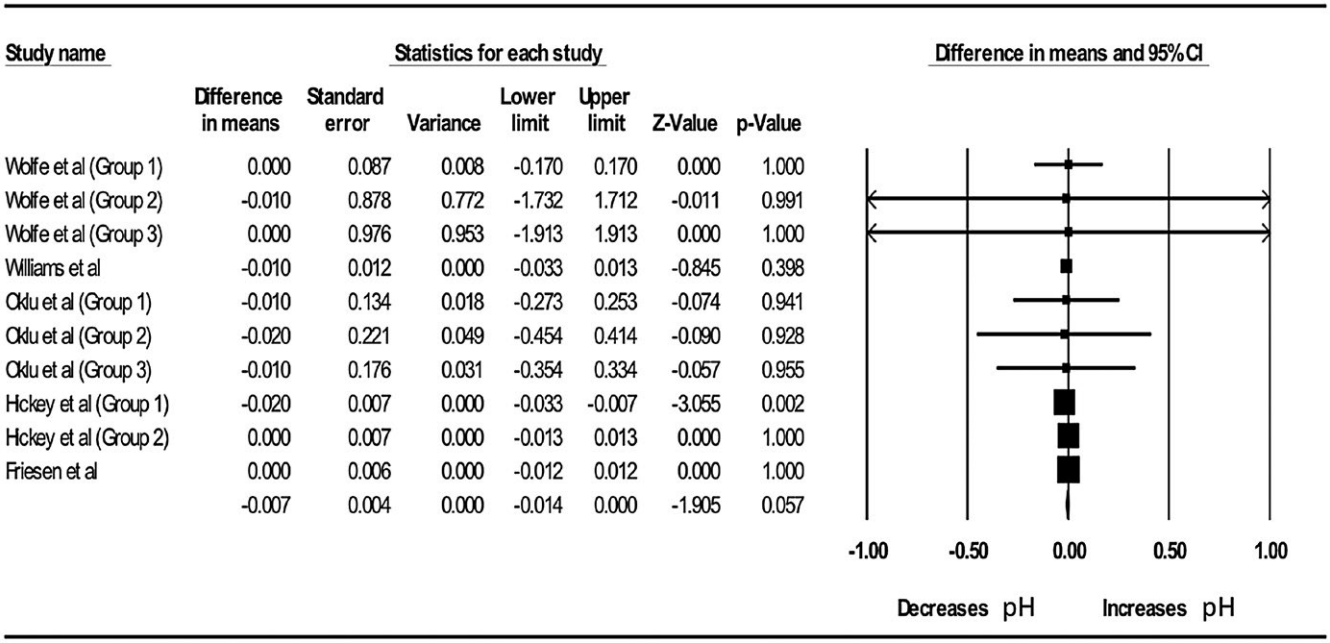

FIGURE 7 Forest plot demonstrating the individual and pooled results for effect of ketamine on blood hydrogen ion concentration (pH)

There was a statistically significant increase in the blood carbon dioxide concentration with the administration of ketamine. The mean difference was found to be 1.38 mm Hg (95% confidence interval 0.35-2.40, P = .008) (Figure 8).

Meta-regression demonstrated the following statistically significant associations: greater decrease in blood carbon dioxide concentration with increasing age and greater increase in blood carbon dioxide concentration with increasing time from ketamine administration. Gender and ketamine dose did not have significant impact on change in blood carbon dioxide concentration.

3.9.1 | Blood oxygen concentration

A total of six studies presented data regarding blood oxygen concentration.[9–14] These provided data from 117 patients. The P value for the Q statistic was .365 and the I^2-statistic was 8% so a fixed-effects model was used to pool these data. An Egger's regression was conducted and resulted in a P value of .041 demonstrating significant publication bias.

There was no statistically significant difference in blood oxygen concentration with the administration of ketamine. The mean

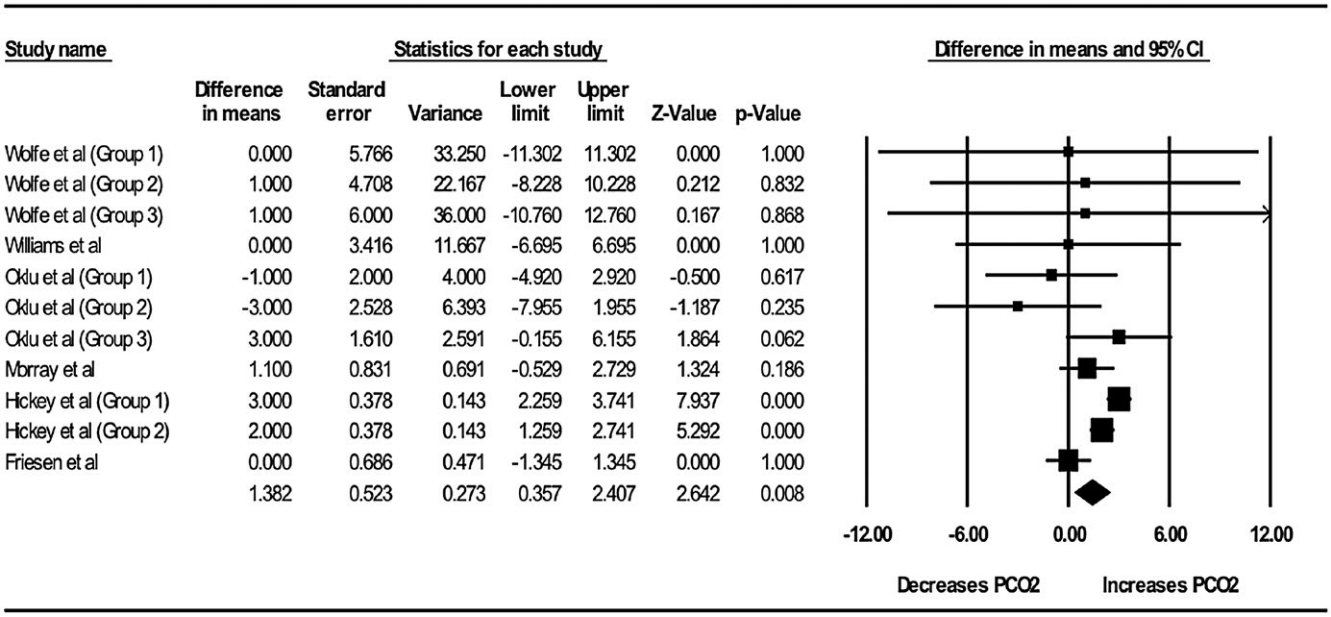

FIGURE 8 Forest plot demonstrating the individual and pooled results for effect of ketamine on blood carbon dioxide concentration (pCO_2)

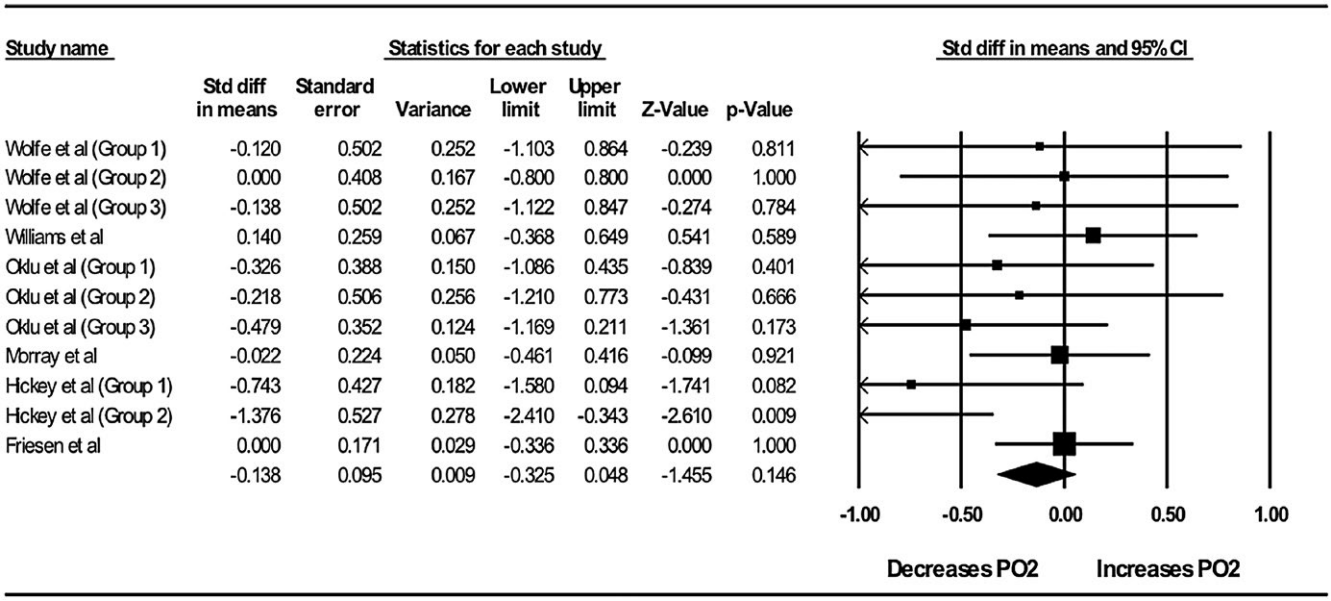

FIGURE 9 Forest plot demonstrating the individual and pooled results for effect of ketamine on blood oxygen concentration (pO_2)

difference was found to be −0.13 (95% confidence interval −0.32 to 0.04, P = .146) (Figure 9).

Meta-regression demonstrated that age, time from ketamine administration, ketamine dose, and gender did not significantly impact the change in blood oxygen concentration.

4 | DISCUSSION

After pooling data from 7 studies with a total of 139 patients with congenital heart disease and/or pulmonary hypertension, ketamine administration was found to have little impact on hemodynamic and blood gas parameters 2-5 minutes after ketamine administration.[9–12,14,16] Systemic vascular resistance, pulmonary vascular resistance, systemic arterial pressure, mean pulmonary artery pressure, cardiac index, heart rate, pH, blood oxygen concentration all remained similar after ketamine administration. The blood carbon dioxide concentration did demonstrate a statistically significant increase after ketamine administration although the increase was less than 2 mm Hg, thus not being clinically significant.

These findings are of note because ketamine is a frequently used sedative in the cardiac intensive care unit, particularly for procedural

sedation. Anecdotally, many practitioners in the cardiac intensive care unit worry about hemodynamic effects of ketamine in children with congenital heart disease, particularly with respect to systemic vascular resistance. For this reason, we set forth to identify the available data for pooling and meta-analysis. Much of the data regarding the cardiovascular effects comes from the adult population which may not be directly applicable to the pediatric population.

The included studies were retrospective in nature and a majority of them were done in the setting of a catheterization laboratory. Two studies were not conducted in this fashion, with one study being conducted in the operating room prior to surgical intervention with surgically placed catheters and the other study being conducted in the intensive care unit utilizing surgically placed catheters. The ketamine dose in the studies was variable as was the time after ketamine administration at which hemodynamic measurements were repeated. To account for these two parameters, meta-regression was utilized to characterize the impact of such variables on the degree of change in the end point of interest.

Meta-regression demonstrated that ketamine dose had a statistically significant impact on the change in mean systemic arterial pressure, cardiac index, and heart rate with all decreasing with increasing dose. Meta-regression also demonstrated that time from ketamine administration also had a statistically significant impact on the change in systemic vascular resistance and blood carbon dioxide level with systemic vascular resistance decreasing with increasing time from ketamine administration and blood carbon dioxide level increasing with increasing time from ketamine administration. Regardless, however, other than the blood carbon dioxide level none of these end points demonstrated significant change after ketamine administration.

Some limitations were identified. For instance, studies included in this study were small and mostly retrospective, with many having limited capacity for adjustment, and thus are at risk of selection bias and residual confounding. Also, studies included had wide variation of cardiac diagnoses, as well as significant heterogeneity in outcomes, which limited our capacity for subgroup analysis in selected circumstances. Each individual study may have had some selection bias. It is hard to ascertain whether or not this was the case but this could certainly be present. For instance, authors may have elected to enroll only patients in the individual studies if they were deemed to be healthier and those with poor cardiac function may have not been administered ketamine and thus enrolled. While the mean cardiac index is provided by several of the included studies it is hard to know how many patients had a lower cardiac index, a surrogate of poor cardiac function. Thus, we are unable to comment on the safety of ketamine in those that have depressed function. Lastly, most populations of cardiac lesions were underrepresented in the included studies, which could limit generalizability of the findings. Many of the studies did not actually provide a breakdown of what lesions were included in what number. This obviously makes it impossible for this pooled analysis to comment on variation of safety or efficacy based on individual lesion. However, this systematic review and meta-analysis is strengthened by the use of a comprehensive search strategy, by rigorous screening and eligibility criteria, and by transparent reporting of our findings.

A future study with a large number of patients in which cardiac function and cardiac lesion are both clearly stated and subset analysis is done for those with more complex lesions and depressed cardiac function can help provide more insight into the safety of ketamine in those with congenital heart disease.

5 | CONCLUSION

This systematic review and meta-analysis did not identify significant hemodynamic differences at approximately 5 minutes after ketamine administration in children with congenital heart disease and/or pulmonary hypertension when used at usual clinical doses. Systemic vascular resistance and pulmonary vascular resistance are not significantly altered and blood gas values are also only minimally affected by ketamine.

CONFLICT OF INTEREST

The authors have disclosed that they do not have any potential conflict of interest.

AUTHOR CONTRIBUTIONS

Rohit Loomba study conception, study design, included study identification, data extraction, data analysis, drafting of manuscript.

Seth Gray included study identification, included study quality review, data extraction, drafting of manuscript.

Saul Flores included study quality review, data review, drafting of manuscript.

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