Cardiology in the Young

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The effect of milrinone on hemodynamic and gas exchange parameters in children

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Original Article

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Abstract

Milrinone is a drug frequently used for hemodynamic support in children during critical illness. Although the hemodynamic changes induced by milrinone in children may appear similar to those of adults, the physiologic contributors of these changes remain vastly unknown. A systematic review was conducted to identify studies characterising the hemodynamic effects of milrinone in children during critical illness for hemodynamic support for various medical conditions. Studies were assessed for quality and those of satisfactory quality with pre- and post-operative hemodynamics for each patient were included in the final analyses. Those not limited to children and those not limited to patients with critical illness were excluded from the final analyses. A total of six studies with 791 patients were included in the final analyses. Milrinone infusion doses ranged from 0.3 to 0.75 mcg/kg/minute with the mean infusion dose being 0.5 mcg/kg/minute. Patients whom received milrinone infusion had greater cardiac output, greater left ventricle shortening fraction, lower right ventricular systolic pressure, and lower serum lactate levels. Systolic blood pressure mean arterial blood pressure and arterial oxygen concentration did not significantly change with administration of milrinone. These results were irrespective of milrinone infusion dose, infusion duration, and study size. Milrinone was found to have several beneficial hemodynamic effects in children during critical illness when used at usual clinical doses.

Milrinone was developed more than 30 years ago as WIN 47203, a non-glycosidic, non-adrenergic cardiotonic agent with a chemical structure analogous to that of amrinone.[1] Milrinone is a potent cardiac bipyridine with inotropic and vasodilator properties carried out by selective inhibition of the cardiac adenosine 3',5'-monophosphate (cAMP) phosphodiesterase III isozyme, with resultant increases in cardiac cAMP levels.[2] The pharmacologic effects of milrinone include relaxation of the smooth muscle, enhanced myocardial contractility, and improved myocardial relaxation.[3,4] The cardiovascular effects of milrinone were initially characterised in animal models and adult humans by increased cardiac output and decreased left ventricular end-diastolic pressure while significantly decreasing systemic vascular resistance.[2,5,6]

Milrinone has been used for a number of years to mitigate the effects of low cardiac output particularly in patients after congenital heart surgery.[7] The hemodynamic changes induced by milrinone in children appear to be similar to those of adults. However, the physiologic contributors of these changes remain vastly unknown. Furthermore, recent trials in children and adults have demonstrated conflicting results related to patient outcomes, medication effectiveness, and the impact on hemodynamics.[8–10] Therefore, the primary objective of this study was to determine the effect of milrinone on hemodynamic parameters in critically ill children by comparing hemodynamic data before and after the initiation of milrinone. A systematic review and subsequent meta-analyses were conducted.

Materials and methods

Study identification

A systematic review was conducted to identify studies pertaining to the hemodynamic effects of milrinone in children. A new review protocol was used for this study as there was no existing protocol. Pubmed, EMBASE, and the Cochrane databases were queried to identify such studies. The following keywords were used in individually and in various combinations with one another: "milrinone," "children," "pediatrics," "hemodynamics," "blood pressure," "cardiac output," "pulmonary artery pressure," and "vascular resistance" (Supplementary File S1). Both authors (RL, SF) reviewed the abstracts and titles of resulting studies. Full-text manuscripts of studies found to be pertinent to study questions were then obtained. These were reviewed for quality using the Newcastle–Ottawa Scale and assessed for risk of bias using the

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Cochrane Risk of Bias tool. Any discrepancies in these evaluations between the two authors were then reviewed by both authors and a consensus achieved. Studies of adequate quality and low risk of bias were then considered for inclusion.

Studies were included in the final pooled analyses if they met the following requirements: (1) utilised milrinone; (2) included children (under 18 years of age); (3) contained data for hemodynamic parameters before and after the initiation of milrinone; (4) published data; and (5) English language. Studies that met these criteria were then deemed appropriate for inclusion. Any discrepancies in appropriateness of inclusion between the two authors were reviewed by both authors and a consensus achieved.

Endpoints

Reported endpoints from the studies deemed appropriate for inclusion were outlined. The number of studies reporting each endpoint were then reviewed and a decision was made to include endpoints that had data from two or more studies. The following endpoints were identified for pooled analyses: systolic blood pressure (mmHg), mean arterial blood pressure (mmHg), echocardiographic Doppler-derived cardiac output (ml/kg/minute), left ventricular shortening fraction (%), right ventricular systolic pressure (mmHg), heart rate (beats per minute), arterial oxygen concentration (mmHg), arterial carbon dioxide concentration (mmHg), fraction of inspired oxygen (%), and serum lactate (mmol/L).

Data extraction

Data were extracted using an electronic data extraction tool. Data were extracted by both authors independently. As all variables were continuous, means and standard deviations for the pre- and post-milrinone data were recorded. The individually extracted data were then compared to identify any discrepancies. Discrepancies in the extracted data were then reviewed by the authors together and discrepancies resolved by consensus.

Bias analysis

Bias analysis was performed with specific attention paid to patient selection, intervention selection, endpoint inclusion, and result reporting.

Statistical analysis

Once data were extracted each endpoint underwent evaluation of heterogeneity. A Q-statistic and its resulting p value were calculated as was an I^2 statistic. If the p value for the Q-statistic was less than 0.05 or if the I^2 value was greater than 50%, heterogeneity was deemed significant. In the absence of significant heterogeneity, a fixed-effects model was used for the pooled analyses while a random-effects model was used if there was significant heterogeneity present. All endpoints were continuous in nature and thus pooled analyses were conducted to determine the mean difference and 95% confidence interval. Publication bias was assessed using an Egger test for endpoints with data from three or more studies. Meta-regression was not conducted due to the low number of pooled studies. Sensitivity analyses were conducted to determine the effect of milrinone dose, duration of milrinone infusion, and study size on the individual endpoints.

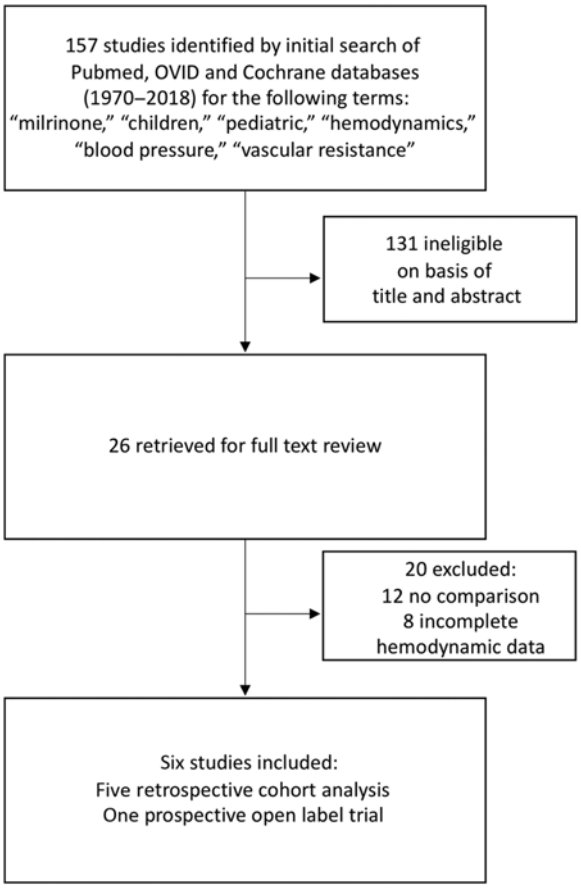

Figure 1. Study identification methodology.

Results

Study characteristics

A total of six studies including 791 patients were included in the analyses (Fig 1).[11–16] Studies were published between the years 2013 and 2018. A majority, four, of the six studies included patients in the first month of life. The mean age of included patients was 8.5 months. Milrinone infusion doses ranged from 0.3 to 0.75 mcg/kg/minute with the mean infusion dose being 0.5 mcg/kg/minute. The duration of milrinone infusion until repeat hemodynamics ranged from 20 to 408 hours with a mean of 119 hours (Table 1).

Systolic blood pressure

A total of five studies with data from 774 patients were included in the pooled analysis of systolic blood pressure. Heterogeneity analysis resulted in a Q-statistic with a p value of less than 0.001 and an I^2 value of 90%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Systolic blood pressure was not significantly different with milrinone infusion. The mean difference in systolic blood pressure was 3.46 mmHg with a 95% confidence interval −1.20 to 8.12 ($p = 0.15$) (Fig 2).

Sensitivity analyses demonstrated that milrinone infusion dose and duration did not impact the pooled result. Study size, however, did. With the removal of data from group A of the study from Lee et al, the change in systolic blood pressure was significantly different with a mean difference of 2.18 mmHg (95% confidence interval 0.36–4.00, $p = 0.02$).

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Table 1. Characteristics of selected studies

	Year	n[1]	Age (months)	Type of study	Mean milrinone infusion dose (mcg[2]/kg[3]/minute)	Duration of milrinone until repeat data gathered (hours)	Reason for admission
Bianchi et al	2015	17	0.1	Prospective	0.75	48	Preoperative and postoperative CHD[4]
James et al (CTY[5])	2015	17	0.1	Retrospective	0.5	20	PPHN[6]
James et al (JOP[7])	2014	7	0.1	Retrospective	0.5	70	PPHN[6]
Kumar et al	2018	12	0.1	Retrospective	0.35	140	Preoperative CHD[4]
Lee et al (group a)	2014	715	9	Retrospective	0.5	120	Postoperative CHD[4]
Lee et al (group b)	2014	12	29.6	Retrospective	0.5	408	Non-surgical HF[8]
McNamara et al	2013	11	0.1	Prospective	0.3	24	PPHN[6]

[1]Sample size, [2]micrograms, [3]kilograms, [4]congenital heart disease, [5]Cardiology in the Young, [6]persistent pulmonary hypertension of the newborn, [7]Journal of Pediatrics, [8]heart failure

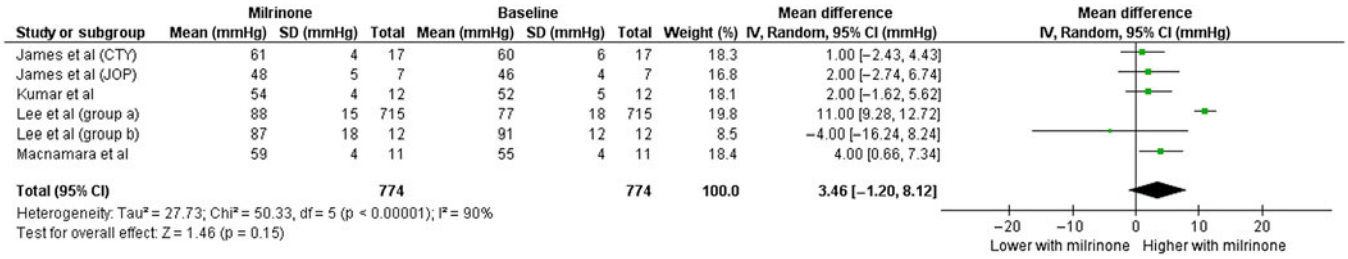

Figure 2. Forest plot demonstrating impact of milrinone on systolic blood pressure.

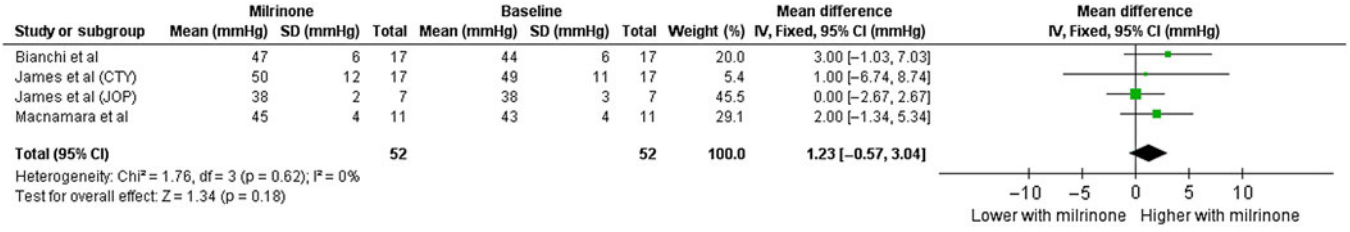

Figure 3. Forest plot demonstrating impact of milrinone on mean arterial blood pressure.

Mean arterial blood pressure

A total of four studies with data from 52 patients were included in the pooled analysis of mean arterial blood pressure.[11–13,16] Heterogeneity analysis resulted in a Q-statistic with a p value of 0.62 and an I^2 value of 0%, indicating the absence of significant heterogeneity. Thus, a fixed-effects model was used. Mean arterial blood pressure was not significantly different with milrinone infusion. The mean difference in mean arterial blood pressure was 1.23 mmHg with a 95% confidence interval −0.57 to 3.04 ($p = 0.18$) (Fig 3).

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Cardiac output

A total of four studies with data from 52 patients were included in the pooled analysis of cardiac output.[11–13,16] Heterogeneity analysis resulted in a Q-statistic with a p value of 0.39 and an I^2 value of 1%, indicating the absence of significant heterogeneity. Thus, a fixed-effects model was used. Cardiac output was significantly different with milrinone infusion. The mean difference in cardiac output was 52.58 ml/kg/minute with a 95% confidence interval 36.98–68.19 ($p < 0.001$) (Fig 4). Thus, cardiac output was significantly greater with milrinone.

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Left ventricular shortening fraction

A total of five studies with data from 219 patients were included in the pooled analysis of left ventricular shortening fraction.[11–15] Heterogeneity analysis resulted in a Q-statistic with a p value of less than 0.001 and an I^2 value of 75%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Left ventricular shortening fraction was significantly different with milrinone infusion. The mean difference in left ventricular

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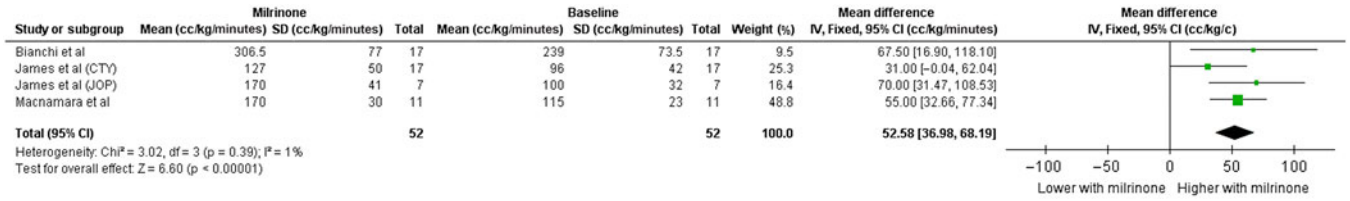

Figure 4. Forest plot demonstrating impact of milrinone on cardiac output.

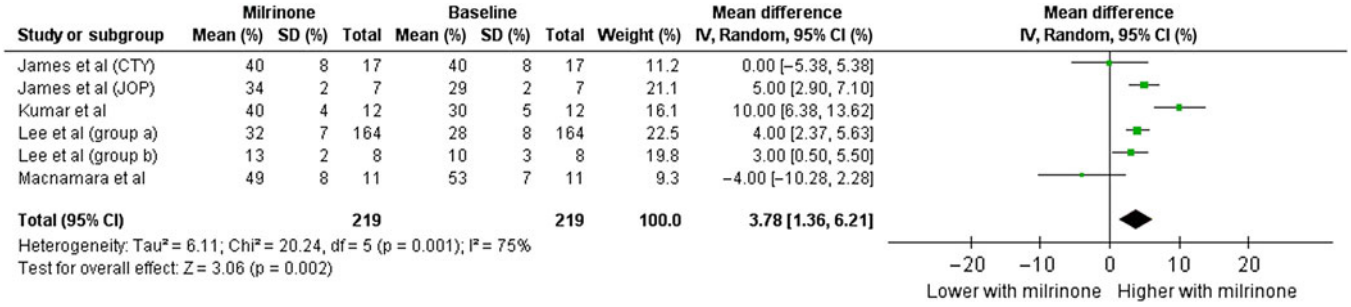

Figure 5. Forest plot demonstrating impact of milrinone on left ventricle shortening fraction.

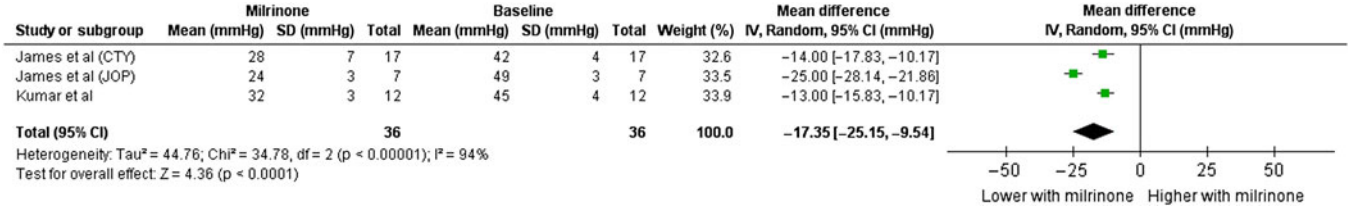

Figure 6. Forest plot demonstrating impact of milrinone on right ventricle systolic pressure.

shortening fraction was 3.78% with a 95% confidence interval 1.36–6.21 (p = 0.002) (Fig 5). Thus, left ventricular shortening fraction was significantly greater with milrinone.

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Right ventricular systolic pressure

A total of three studies with data from 36 patients were included in the pooled analysis of right ventricular systolic pressure. Heterogeneity analysis resulted in a Q-statistic with a p value of <0.001 and an I^2 value of 94%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Right ventricular systolic pressure was significantly different with milrinone infusion. The mean difference in right ventricular systolic pressure was −17.35 mmHg with a 95% confidence interval −25.15 to −9.54 (p < 0.001) (Fig 6). Thus, right ventricular systolic pressure was significantly lower with milrinone.

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Heart rate

A total of four studies with data from 772 patients were included in the pooled analysis of heart rate. Heterogeneity analysis resulted in a Q-statistic with a p value of less than 0.001 and an I^2 value of 94%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Heart rate was significantly different with milrinone infusion. The mean difference in heart rate was −5.14 beats per minute with a 95% confidence interval −16.00 to 5.73 (p = 0.35) (Fig 7).

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Arterial oxygen concentration

A total of five studies with data from 774 patients were included in the pooled analysis of arterial oxygen concentration. Heterogeneity analysis resulted in a Q-statistic with a p value of less than 0.001 and an I^2 value of 90%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Arterial oxygen concentration was not significantly different with milrinone infusion. The mean difference in arterial oxygen

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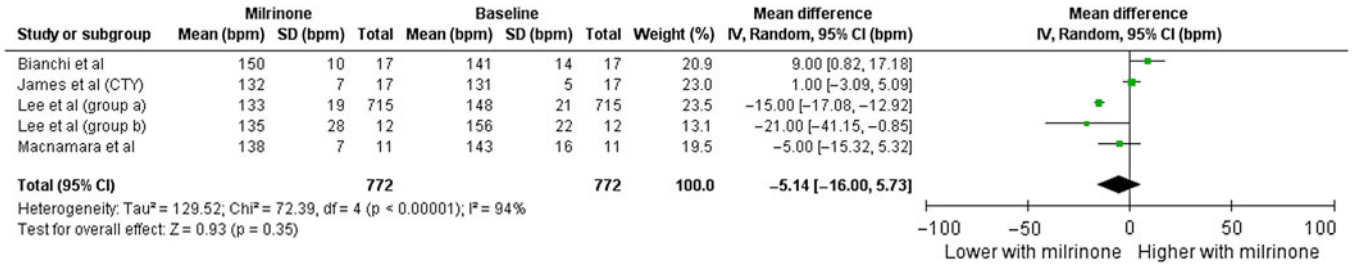

Figure 7. Forest plot demonstrating impact of milrinone on heart rate.

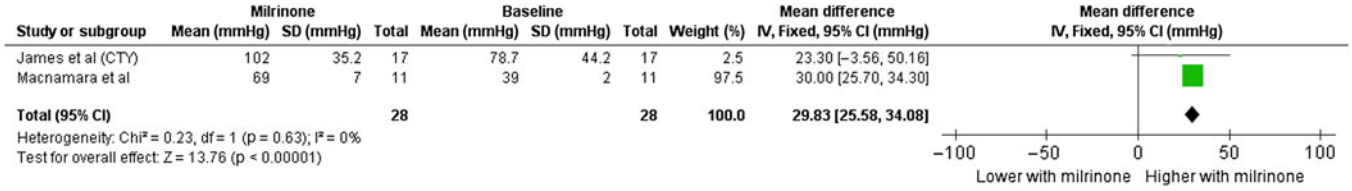

Figure 8. Forest plot demonstrating impact of milrinone on arterial concentration of oxygen.

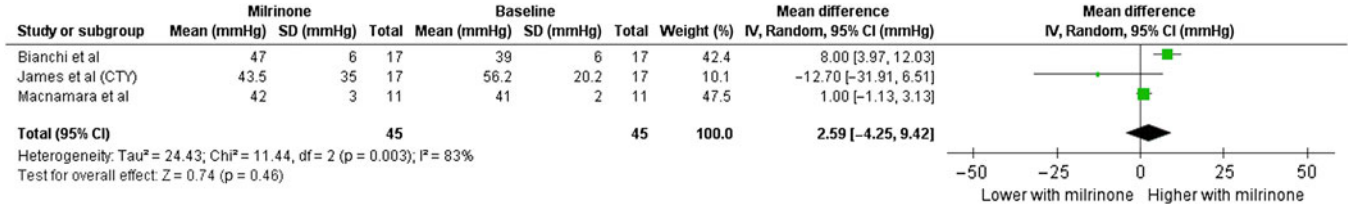

Figure 9. Forest plot demonstrating impact of milrinone on arterial concentration of carbon dioxide.

concentration was 3.46 mmHg with a 95% confidence interval −1.20 to 8.12 (p = 0.15) (Fig 8).

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Arterial carbon dioxide concentration

A total of three studies with data from 45 patients were included in the pooled-analysis of arterial carbon dioxide concentration.[12,13,16] Heterogeneity analysis resulted in a Q-statistic with a p value of less than 0.001 and an I^2 value of 83%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Arterial carbon dioxide concentration was not significantly different with milrinone infusion. The mean difference in arterial carbon dioxide concentration was 2.59 mmHg with a 95% confidence interval −4.25 to 9.42 (p = 0.46) (Fig 9).

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Fraction of inspired oxygen

A total of three studies with data from 35 patients were included in the pooled analysis of fraction of inspired oxygen. Heterogeneity analysis resulted in a Q-statistic with a p value of less than 0.001 and an I^2 value of 97%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Fraction of inspired oxygen was not significantly different with milrinone infusion. The mean difference in fraction of inspired oxygen was −16.52 with a 95% confidence interval −47.15 to 14.12 (p = 0.29) (Fig 10).

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

Serum lactate

A total of three studies with data from 45 patients were included in the pooled analysis of serum lactate.[12,13,16] Heterogeneity analysis resulted in a Q-statistic with a p value of less than 0.001 and an I^2 value of 97%, indicating the presence of significant heterogeneity. Thus, a random-effects model was used. Serum lactate was significantly different with milrinone infusion. The mean difference in serum lactate was −1.77 mmol/L with a 95% confidence interval −3.01 to −0.52 (p < 0.001) (Fig 11). Thus, serum lactate was significantly lower with milrinone.

Sensitivity analyses demonstrated that milrinone infusion dose, milrinone infusion duration, and study size did not impact the pooled result.

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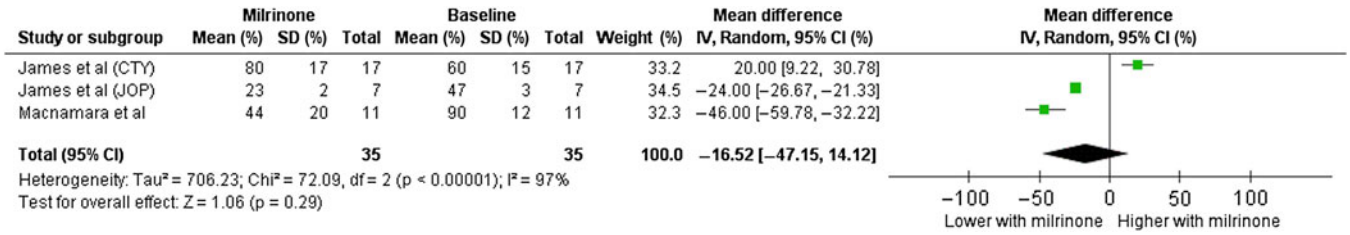

Figure 10. Forest plot demonstrating impact of milrinone on fraction of inspired oxygen.

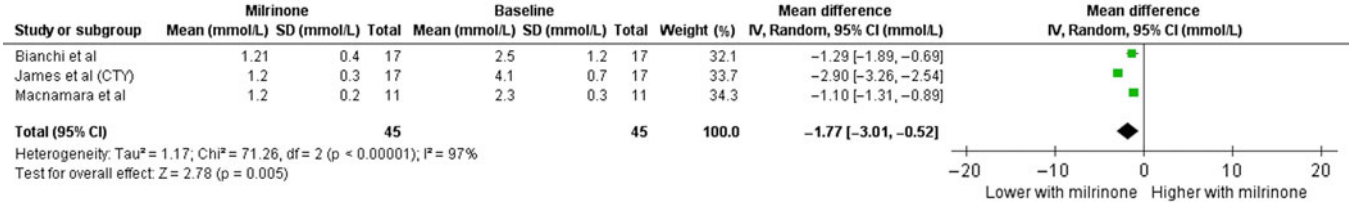

Figure 11. Forest plot demonstrating impact of milrinone on serum lactate.

Discussion

The pooled analysis from six studies contains data for 791 critically ill children with various medical conditions in whom hemodynamic data were captured before and after the initiation of milrinone infusion. Milrinone was found to have several beneficial hemodynamic effects. In terms of cardiac function, the pooled analysis demonstrated that patients whom received milrinone infusion had greater cardiac output, greater left ventricle shortening fraction, and lower right ventricular systolic pressure. It was not surprising to also identified lower heart rate in these patients likely due to a concurrent cardiac output increase during milrinone infusion. Similarly, the pooled analysis demonstrated lower serum lactate levels in patients who received milrinone, presumably as a consequence of better oxygen delivery following cardiac output augmentation.

In terms of blood pressure, although the pooled analysis did not demonstrate a significant difference in systolic or mean arterial blood pressure, sensitivity analyses allowed to uncover a difference in systolic blood pressure of 2.18 mmHg. However, the implications of this difference may not be clinically significant. Furthermore, some of the studies observed echocardiographic changes related to a decrease of pulmonary vascular resistance, but the lack of objective data in the included studies limits our ability to expand further.[11,12]

The pooled analysis also demonstrated no difference with regards to arterial oxygen concentration, arterial carbon dioxide concentration, and the fraction of inspired oxygen. Collectively, these findings may demonstrate that the physiologic benefits observed with milrinone are primarily related to cardiac output augmentation.

Five of the included studies in this meta-analysis were retrospective in nature and took place in a critical care setting, where patients required vasoactive support for various conditions. The study completed by McNamara et al was the only prospective interventional study found in the literature. This study was primarily set up to obtain pharmacodynamic and pharmacokinetic data of milrinone in children with persistent pulmonary hypertension of the newborn and the hemodynamic information was obtained as a secondary assessment.[13] Two more of the included studies were conducted in children with persistent pulmonary hypertension of the newborn.[11–13] Together, these studies identified a modest decrease in right ventricular systolic pressure with no changes in systolic blood pressure, mean arterial blood pressure, or fraction of inspired oxygen. These findings are important, particularly because most of the positive effects seen from milrinone were not impacted by the infusion dose, infusion duration, and study size.

This systematic review and meta-analysis is strengthened by the use of a comprehensive search strategy, by rigorous screening and eligibility criteria and transparent reporting of our findings. However, the studies included in this manuscript were mainly retrospective, relatively small, and not powered to estimate any specific hemodynamic changes. In addition, the studies included had a wide array of diagnoses, as well as significant heterogeneity in hemodynamic outcomes, which limited our capacity for subgroup analyses in selected circumstances. The estimation of cardiac output was derived in most studies from echocardiography which is heavily dependent on loading conditions and contains inherit limitations. Some of the studies included in the meta-analysis had simultaneous cointerventions during the study time; therefore, some of the effects of milrinone may have been potentiated by synergism. Finally, the inclusion of studies with a difference in patient population, diagnosis, and management could limit generalisability of the findings.

Conclusion

The findings from this systematic review and meta-analysis identified significant hemodynamic differences after initiation of milrinone infusions in critically ill children with various medical conditions. Cardiac output, left ventricle shortening fraction, and lower right ventricular systolic pressure are significantly altered, whereas a difference in systolic blood pressure was only uncovered after excluding smaller studies. There was no difference in the fraction of inspired oxygen and the arterial oxygen and carbon dioxide concentration.

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Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951119002865

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Conflicts of Interest. None.

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