BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

CORRESPONDENCE

Improved oxygenation with inhaled milrinone in mechanically ventilated patients with severe COVID-19

Dominik J. Vogel[1,*], Aimee Brame[1], Fraser Hanks[1,2], Chris Remmington[1,2], Natali Chung[3] and Luigi Camporota[1,4]

[1]Intensive Care Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK, [2]Pharmacy Department, Guy's and St Thomas' NHS Foundation Trust, London, UK, [3]Adult Congenital Heart Disease Service, Guy's and St Thomas' NHS Foundation Trust, London, UK and [4]Centre of Human Applied Physiological Sciences, King's College London, London, UK

*Corresponding author. E-mail: dominik.vogel@gstt.nhs.uk

Keywords: acute respiratory distress syndrome; COVID-19; hypoxaemia; milrinone; phosphodiesterase 3 inhibitor; pulmonary vasodilator

Editor—Patients with COVID-19 acute respiratory distress syndrome (C-ARDS) present with severe hypoxaemia that may be disproportionate to the loss in aerated lung.[1] The main mechanism of hypoxaemia has been attributed to a dysregulated pulmonary perfusion, and therefore, inhaled pulmonary vasodilators have been used to improve gas exchange in these patients.[2] However, during the COVID-19 pandemic, the significant increase in C-ARDS resulted in national supply chain shortages of inhaled vasodilators, such as iloprost, epoprostenol, and nitric oxide. Besides the limited availability, these drugs are costly: nitric oxide (£665 per day), iloprost (£60–120 per day), and epoprostenol (£45–75 per day). Milrinone, a phosphodiesterase 3 inhibitor that has shown benefit to improve oxygenation in patients with pulmonary hypertension, is a widely available and less costly alternative (£13 per day), but data in ARDS are scarce.[3–6] During the pandemic, we hypothesised that in mechanically ventilated patients with C-ARDS with a Pa_{O_2}/FiO_2 ratio <20 kPa, inhaled milrinone would improve oxygenation and reduce physiological dead-space fraction, and we therefore used inhaled milrinone as an alternative vasodilator during the drug shortages.

We describe the first 14 patients who received inhaled milrinone (2.5–5 mg every 6 h) for ≥12 h. Milrinone was administered via mesh nebulisation in accordance with departmental guidance, but at the discretion of the clinical team. We retrieved data on ventilation and blood gas analyses from electronic records, and calculated oxygenation index (OI), Pa_{O_2}/FiO_2, and three indices of dead-space ventilation (end-tidal CO_2/Pa_{CO_2}, ventilatory ratio, and corrected minute ventilation).[7–9] Values were recorded before first milrinone dose, 1–2 h after, and subsequently at 6 and 12 h. The closest temporally associated transthoracic echocardiograms obtained before and after initiation were reviewed by a consultant cardiologist for indices of right ventricle (RV) and left ventricle (LV) size and function.[10] Records were reviewed for potentially related adverse events, including haemodynamic instability, deterioration in gas exchange, dose adjustments, or early termination of therapy.

Continuous data were tested for normal distribution (Shapiro–Wilk test). Normally distributed data are presented as mean (standard deviation [SD]), not normally distributed data as median (inter-quartile range [IQR]), and nominal data as number (%). One-way repeated-measures analysis of variance was used to compare means across different time points. Observed differences to baseline are provided as means and 95% confidence interval (95% CI). *Post hoc* Bonferroni correction was applied to account for multiple comparisons when comparing individual pairs of groups. For comparison of means, *t*-test was used for parametric data.

A local guidance document for the use of inhaled milrinone was approved by the trust Drug and Therapeutics Committee. Institutional approval was gained from the local audit committee (project reference 11146). The need for individual informed consent was waived for this retrospective analysis of data collected prospectively for routine care, without breach of

privacy or anonymity. The study qualified as a service evaluation as defined by the UK NHS Health Research Authority, and therefore did not require review by a research ethics committee.

The 14 patients had a mean (SD) age of 62.6 (6.9) yr. Admission Acute Physiology and Chronic Health Evaluation II was 17 (IQR: 13.8–18.5), 10 were male (71.4%) and had a BMI 29.0 (6.6) kg m^{-2}. Patients had been ventilated for 20.6 (15.5) days before initiation of milrinone. At baseline (pre-milrinone), patients had a Sequential Organ Failure Assessment score of 7.5 (IQR: 5–12.5), received tidal volume of 5.8 (1.9) ml kg^{-1} predicted body weight, PEEP 8 (IQR: 6–10) cm H_2O, peak pressure 30 (3) cm H_2O, and had a dynamic compliance of 20 (IQR: 15–22) ml cm H_2O^{-1}. Mean Pa_{o2}/FiO_2 at baseline was 11.6 (1.6) kPa, and 6/14 (42.9%) were proned. At baseline, 2/12 (16%) had impaired longitudinal RV function (tricuspid annular plane systolic excursion [TAPSE] <17 mm), 3/12 (25%) a dilated RV (RV end-diastolic basal diameter >43 mm [female] or >47 mm [male]), and 3/12 (25%) RV/LV ratio >1; none of the patients had impaired LV function (LV ejection fraction <50%). Another pulmonary vasodilator had been used in 5/14 (35.7%) patients before starting milrinone.

There was a significant main effect of inhaled milrinone on $Pa_{o_2/FiO2}$ ($P<0.01$) and OI ($P<0.001$), in the first 12 h (Fig. 1). This improvement was statistically significant (after correction for multiple comparisons) for Pa_{o2}/FiO_2 post-6 h dose (mean difference to baseline +2.7 kPa; 95% CI: 0.3–5.0; $P<0.05$) and post-12 h dose (+3.1 kPa; 95% CI: 0.8–5.4; $P<0.01$), and for OI post-6 h dose (−3.2; −0.12 to −6.2; $P<0.01$) and 12 h dose (−4.0; 95% CI: −0.5 to −7.6; $P<0.01$ [lower OI reflects improved Pa_{o2}, or similar Pa_{o2} for lower applied mean airway pressure or FiO_2]). During this observation time, no additional patient received prone positioning.

For patients in whom milrinone was continued for ≥48 h ($n=7$), the improvement in Pa_{o2}/FiO_2 was maintained, and this was higher by +3.9 kPa (95% CI: 0.6–7.2; $P<0.05$) and OI was lower by −5.1 (95% CI: −0.5 to −9.7; $P<0.05$) post-48 h dose compared with baseline, respectively.

There was a greater improvement in Pa_{o2}/FiO_2 compared with baseline post-6 h dose in the group with a shorter duration of mechanical ventilation (<20 days; $n=7$), compared with those who had been ventilated longer (>20 days; $n=7$) before receiving the first dose (mean difference +26.3%; 95% CI: 0.8–51.9%; $P<0.05$). These patients had high indices of dead space with end-tidal CO_2/Pa_{co2} 0.67 (0.12), ventilatory ratio 2.37 (1.17), and corrected minute volume 14.13 (6.1) L min^{-1}. However, there was no change in dead space after milrinone (end-tidal CO_2/Pa_{co2} 0.70 [0.12], ventilatory ratio 2.62 [1.12], and corrected minute ventilation 15.5 [7.4] L min^{-1} at 12 h).

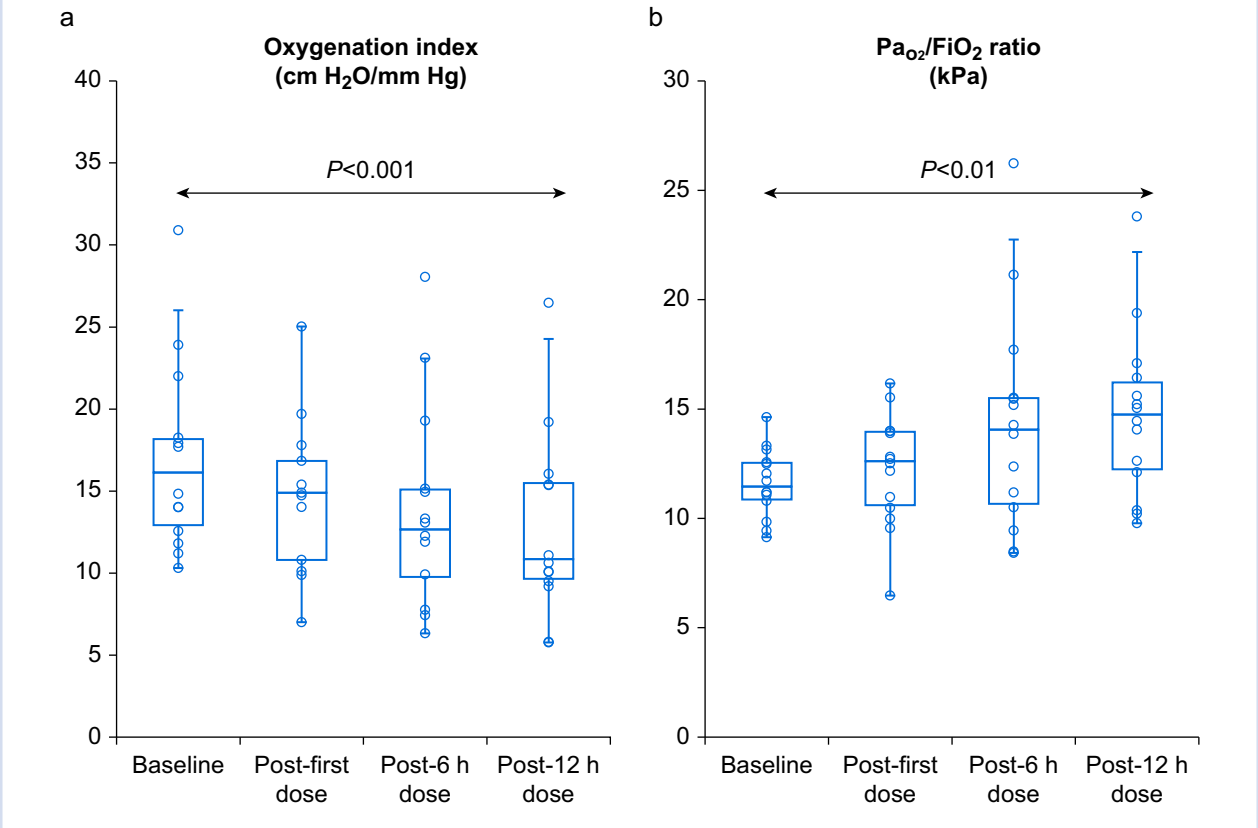

Fig 1. Box and whisker plot of indices of oxygenation: (a) Oxygenation Index (OI = mean airway pressure(cm H_2O) × FiO_2 × 100/Pa_{o_2} (mm Hg)) and (b) Pa_{o_2}/FiO_2 ratio (kPa). Lower OI reflects improved arterial oxygenation, or similar oxygenation for lower applied mean airway pressure or FiO_2. There was a significant main effect of inhaled milrinone on Pa_{o_2}/FiO_2 ratio ($P<0.01$) and OI ($P<0.001$), comparing all obtained values until and including the post-12 h dose ($n=14$ for each time point). The ends of the whiskers are set at 1.5× inter-quartile range above the third quartile and below the first quartile, or the minimum or maximum value if within these limits. All values are shown as circles.

For patients in whom comparable studies were available, there was no significant difference in TAPSE (n=9; 19 [6] and 19 [5] mm), RV diameter (n=9; 3.8 [1.1] and 3.6 [0.8]), or RV/LV ratio (n=7; 0.88 [0.2] and 0.87 [0.1]) before and after milrinone, respectively.

No adverse events were observed during the patients' ICU admission. A transient deterioration in oxygenation (<6 h) was noted in one patient, but coincided with the development of a new ventilator-associated pneumonia.

These results show that milrinone might be a useful alternative to inhaled nitric oxide, epoprostenol, or iloprost for improving oxygenation even late in the course of C-ARDS, and at this late stage milrinone did not affect dead-space ventilation. It is likely that given the duration of the disease and the low compliance, the predominant mechanism of hypoxaemia in these patients was venous admixture secondary to consolidation or fibrosis, and may explain why the physiological dead space was unmodified. These results are based on observational data from a case series and need to be interpreted in this context. The effects of milrinone on dead space could be tested earlier in the disease, where functional vasoconstriction of ventilated areas can affect physiological dead space.

We conclude that in mechanically ventilated patients with severe COVID-19, inhaled milrinone was associated with improved oxygenation for up to 48 h of administration.

Declarations of interest

The authors declare that they have no conflicts of interest.

References

1. Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. *Intensive Care Med* 2020; **46**: 2187–96
2. The Faculty of Intensive Care Medicine (FICM) and The Intensive Care Society (ICS). Clinical guide for the management and care of critically ill adults with COVID-19 during the coronavirus pandemic. Available from: https://static1.squarespace.com/static/5e6613a1dc75b87df82b78e1/t/60800b8100361404e3e37493/1619004290257/Clinical+guide_FINAL_MG_16-4-21.pdf (accessed 1 May 2021).
3. Haraldsson SA, Kieler-Jensen N, Ricksten SE. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. *Anesth Analg* 2001; **93**: 1439–45
4. Theodoraki K, Thanopoulos A, Rellia P, et al. A retrospective comparison of inhaled milrinone and iloprost in post-bypass pulmonary hypertension. *Heart Vessels* 2017; **32**: 1488–97
5. Albert M, Corsilli D, Williamson DR, et al. Comparison of inhaled milrinone, nitric oxide and prostacyclin in acute respiratory distress syndrome. *World J Crit Care Med* 2017; **6**: 74–8
6. Nguyen AQ, Denault AY, Théoret Y, Perrault LP, Varin F. Inhaled milrinone in cardiac surgical patients: a pilot randomized controlled trial of jet vs. mesh nebulization. *Sci Rep* 2020; **10**: 2069
7. Gajic O, Afessa B, Thompson BT, et al. Prediction of death and prolonged mechanical ventilation in acute lung injury. *Crit Care* 2007; **11**: R53
8. Sinha P, Calfee CS, Beitler JR, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2019; **199**: 333–41
9. Vasques F, Sanderson B, Formenti F, Shankar-Hari M, Camporota L. Physiological dead space ventilation, disease severity and outcome in ventilated patients with hypoxaemic respiratory failure due to coronavirus disease 2019. *Intensive Care Med* 2020; **46**: 2092–3
10. Zaidi A, Knight DS, Augustine DX, et al. Echocardiographic assessment of the right heart in adults: a practical guideline from the British Society of Echocardiography. *Echo Res Pract* 2020; **7**: G19–41

doi: 10.1016/j.bja.2021.06.002