

Prospective Study

## Comparison of inhaled milrinone, nitric oxide and prostacyclin in acute respiratory distress syndrome

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### Abstract

#### AIM

To evaluate the safety and efficacy of inhaled milrinone in acute respiratory distress syndrome (ARDS).

#### METHODS

Open-label prospective cross-over pilot study where fifteen adult patients with hypoxemic failure meeting standard ARDS criteria and monitored with a pulmonary artery catheter were recruited in an academic 24-bed medico-surgical intensive care unit. Random sequential administration of iNO (20 ppm) or nebulized epoprostenol (10 µg/mL) was done in all patients. Thereafter, inhaled milrinone (1 mg/mL) alone followed by inhaled milrinone in association with inhaled nitric oxide (iNO) was administered. A jet nebulization device synchronized with the mechanical ventilation was used to administer the epoprostenol and the milrinone. Hemodynamic measurements and partial pressure of arterial oxygen (PaO<sub>2</sub>) were recorded before and after each inhaled therapy

administration.

## RESULTS

The majority of ARDS were of pulmonary cause ( $n = 13$ ) and pneumonia ( $n = 7$ ) was the leading underlying initial disease. Other pulmonary causes of ARDS were: Post cardiopulmonary bypass ( $n = 2$ ), smoke inhalation injury ( $n = 1$ ), thoracic trauma and pulmonary contusions ( $n = 2$ ) and aspiration ( $n = 1$ ). Two patients had an extra pulmonary cause of ARDS: A polytrauma patient and an intra-abdominal abscess. Inhaled nitric oxide, epoprostenol, inhaled milrinone and the combination of inhaled milrinone and iNO had no impact on systemic hemodynamics. No significant adverse events related to study medications were observed. The median increase of PaO<sub>2</sub> from baseline was 8.8 mmHg [interquartile range (IQR) = 16.3], 6.0 mmHg (IQR = 18.4), 6 mmHg (IQR = 15.8) and 9.2 mmHg (IQR = 20.2) respectively with iNO, epoprostenol, inhaled milrinone, and iNO added to milrinone. Only iNO and the combination of inhaled milrinone and iNO had a statistically significant effect on PaO<sub>2</sub>.

## CONCLUSION

When comparing the effects of inhaled NO, milrinone and epoprostenol, only NO significantly improved oxygenation. Inhaled milrinone appeared safe but failed to improve oxygenation in ARDS.

**Key words:** Inhaled milrinone; Nitric oxide; Pulmonary hypertension; Hypoxemia; Acute respiratory distress syndrome; Prostacyclin

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**Core tip:** To our knowledge, this is the first study testing inhaled milrinone as a therapy in acute respiratory distress syndrome and comparing it to more frequently used inhaled therapies. It shows that inhaled milrinone is safe but is not efficacious.

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## INTRODUCTION

Acute respiratory distress syndrome (ARDS) is unfortunately a common problem in intensive care units (ICU) and has been associated with significant morbidity and mortality<sup>[1]</sup>. Hypoxemia and hypercapnia are the primary manifestations of the ventilation-perfusion mismatch observed in ARDS patients. Despite several advances in mechanical ventilation, treatment of severe hypoxemia has remained one of the greatest challenges

in the ICU. Among these therapies, inhaled nitric oxide (iNO) is commonly used for the treatment of hypoxemia in ARDS because it allows for selective vasodilation of ventilated units, transforming relative dead space into adequate ventilation-perfusion units<sup>[1,2]</sup>. Regardless of the well documented failure to improve survival, iNO is still of common use because of the oxygenation gain it allows. However, it has substantial cost, has been associated with potential serious side effects such as renal failure and needs a special device for its delivery<sup>[2,3]</sup>. Inhaled prostacyclin has also been used in ARDS and has been shown to significantly reduce pulmonary artery pressure and increase oxygenation<sup>[4-6]</sup>. However, prostacyclin administration is technically challenging given its short half-life and susceptibility to photo-degradation<sup>[7]</sup>. The phosphodiesterase type III inhibitor milrinone is a potent pulmonary vasodilator that has been used with success as an inhaled therapy for pulmonary hypertension in cardiac surgery and may be a potential alternative to actual treatment strategies<sup>[8,9]</sup>. Animal studies have suggested a response to milrinone in acute lung injury<sup>[10]</sup>.

The primary objective of this study was to assess the tolerability and safety of inhaled milrinone in ARDS patients. The secondary objectives included: Evaluation of the efficacy of inhaled milrinone in improving hypoxemia compared to baseline; comparison of the effects of inhaled milrinone, iNO and inhaled epoprostenol in improving hypoxemia and secondary pulmonary hypertension compared to baseline; evaluation of the efficacy of combining inhaled milrinone with iNO on hypoxemia and pulmonary hypertension.

## MATERIALS AND METHODS

In an academic 24-bed medico-surgical intensive care unit, patients were screened over a 2-year period. Adult patients were enrolled if they had hypoxemic respiratory failure meeting standard moderate to severe ARDS criteria: Ratio of the partial pressure of arterial oxygen (PaO<sub>2</sub>) to the fraction of inspired oxygen (FiO<sub>2</sub>) of 200 or less, pulmonary capillary wedge pressure (Pcwp) ≤ 18 mmHg and bilateral infiltrates on frontal chest radiograph. Recruited patients also had a pulmonary artery catheter and an arterial line. Patients with severe hemodynamic instability (defined as the need for more than one vasopressor or the use of more than 0.5 µg/kg per minute of norepinephrine), on intravenous milrinone or nitrate derivatives that could not be weaned for study purposes and patients on high frequency oscillatory ventilation were excluded. Patients with a history of hypersensitivity to study medications, pregnant patients and those who participated in another study involving oxymetric values or pulmonary hemodynamics were also excluded.

Patients were randomly administered sequential nebulization of iNO (20 ppm) or epoprostenol (10 µg/mL for a total volume of 5 mL). Thereafter, milrinone (1 mg/mL for a total volume of 5 mL at each nebulisation)

**Table 1 Baseline characteristics of the patients (*n* = 15)**

Age (yr)	57 (IQR = 22)
Gender	12 men, 3 women
SOFA score (ICU admission)	7.5 (IQR = 7)
SOFA score (day of protocol)	10.0 (IQR = 5)
APACHE-II (ICU admission)	23 (IQR = 7)
APACHE-II (day of protocol)	23.5 (IQR = 7.0)
PaO <sub>2</sub> (mmHg)	80 (IQR = 39)
FiO <sub>2</sub> (%)	80 (IQR = 30)
PaO <sub>2</sub> /FiO <sub>2</sub>	138 (IQR = 68)
PEEP (cm H <sub>2</sub> O)	10 (IQR = 2)
MAP (mm Hg)	75 (IQR = 16)
mPAP (mm Hg)	28 (IQR = 7)
Cardiac index (L/min per square metre)	3.7 (IQR = 2.6)

IQR: Interquartile range; SOFA: Sequential organ failure assessment; APACHE: Acute physiological and chronic health evaluation; PEEP: Positive end-expiratory pressure; MAP: Mean arterial pressure; mPAP: Mean pulmonary arterial pressure.

alone and in association with iNO was administered. Each drug was nebulized for 20 min and a 30 min washout was allowed between each drug. We used a jet nebulization device ventilator synchronized to nebulize epoprostenol and milrinone (MicroMist® Nebulizer model 1880; Hudson RCI, Temecula, CA, United States). The nebulizer was attached to the inspiratory limb of the ventilator near the endotracheal tube. The mass median diameter obtain with this nebulizer is 2.1 µm and the nebulization flow is between 0.25 and 0.3 mL/min. The ventilatory circuit humidification was stopped during the nebulization. Adjustment of the tidal volume was done during nebulization to obtain the same minute ventilation. The iNO was administered using a standard iNO Delivery system (INOvent®, Ohmeda, Madison, WI, United States) attached to the inspiratory limb of the ventilator. A constant dose of 20 ppm of iNO was used and monitored by the injection device. Blood pressure and oxygenation status were continuously monitored. If hemodynamic instability occurred, defined as a lowering of systolic arterial pressure  $\geq 10$  mmHg or lowering of mean arterial pressure (MAP)  $\geq 5$  mmHg, the study medication was stopped. If oxygenation status worsened, defined as a lowering of arterial oxygen saturation  $\geq 10\%$  (measured with continuous pulse oximetry and confirmed by arterial gas), the study medication was stopped. Adverse events potentially related to study medications such as increase hemodynamic instability and renal failure was prospectively evaluated. Using a previously published milrinone assay<sup>[11]</sup>, we determined the plasma level of milrinone at the end of the administration of inhaled milrinone or the combination of iNO and inhaled milrinone in eight samples from our last four patients.

Demographic data, APACHE II and SOFA scores were collected. The following parameters were measured before and during each specific drug nebulization: MAP, mean pulmonary arterial pressure, thermodilution cardiac output, PaO<sub>2</sub>, heart rate, central venous pressure and Pcw. The following parameters were calculated: Systemic

and pulmonary vascular resistances (SVR and PVR), PVR/SVR Ratio, indexed pulmonary vascular resistance, transpulmonary gradient, PaO<sub>2</sub>/FiO<sub>2</sub>, cardiac index, shunt and oxygenation index. A patient was considered a responder to study medications if is PaO<sub>2</sub> increased of more than 20% from the pre-inhalation value<sup>[2]</sup>.

As the primary goal of this pilot study was safety and feasibility and no preliminary data existed in this population, a convenience sample of 15 patients was chosen. Given a within patient standard deviation of 11%, the sample size enabled the detection of a 12% difference in PaO<sub>2</sub> between baseline and post-milrinone PaO<sub>2</sub>. Given the small sample-size, demographic and baseline data were described as medians and inter-quartile range. Continuous data were analysed using Wilcoxon signed rank tests.

The study was performed at Hôpital du Sacré-Coeur de Montréal, Canada. The local ethics committee approved the protocol and consent was obtained from patients or their next of kin. The protocol was submitted to and approved by Health Canada.

## RESULTS

Fifteen consecutive patients were included in the study (Table 1). The majority of ARDS cases were of pulmonary origin (*n* = 13) and pneumonia (*n* = 7) was the leading underlying initial disease. Other pulmonary causes of ARDS were: Post cardiopulmonary bypass (*n* = 2), smoke inhalation injury (*n* = 1), thoracic trauma and pulmonary contusions (*n* = 2) and aspiration (*n* = 1). Two patients had an extra pulmonary cause of ARDS: A polytrauma patient and an intra-abdominal abscess. The main hemodynamic responses are summarized in Table 2. iNO, epoprostenol, inhaled milrinone and the combination of inhaled milrinone and iNO did not have any significant impact on measured hemodynamics when compared to baseline (all *P* > 0.1).

We observed for the oxygenation measurement a median increase of PaO<sub>2</sub> from baseline of 8.8 mmHg [interquartile range (IQR) = 16.3], 6.0 mmHg (IQR = 18.4), 6 mmHg (IQR = 15.8) and 9.2 mmHg (IQR = 20.2) respectively with iNO, epoprostenol, inhaled milrinone, and iNO added to milrinone. When compared to baseline, the combination of inhaled milrinone and iNO (*P* = 0.004) and only iNO had a statistically significant effect (*P* = 0.036). The median percent response to iNO, epoprostenol, inhaled milrinone and the combination of milrinone and iNO was 11.2% (IQR = 25%), 5.3% (IQR = 24%), 7.9% (IQR = 19%) and 11.8% (IQR = 26%), respectively. The response rate to study medications, defined as an increase of more than 20% from the pre-inhalation value, were 33.3%, 20.0%, 13.3% and 33.3% respectively with iNO, epoprostenol, inhaled milrinone and the combination of inhaled milrinone and iNO. The median PaO<sub>2</sub> response of 39.0 mmHg in responders was higher with iNO than with epoprostenol (26.5 mmHg) or milrinone (10 mmHg).

No significant adverse events related to study medi-

**Table 2 Hemodynamic parameter variations (*n* = 15)**

	iNO	Epoprostenol	Milrinone	Milrinone + NO
MAP (mmHg)	-2.0 (11.0)	1.0 (8.0)	3.0 (6.0)	3.0 (7.0)
HR (bpm)	-2.0 (6.0)	0.0 (4.0)	0.0 (4.0)	0.0 (6.0) <sup>1</sup>
CVP (mmHg)	0.0 (1.4)	0.0 (4.0)	0.0 (1.0)	-1.0 (2.0)
PAOP (mmHg)	0.0 (3.0)	1.0 (4.0)	0.0 (2.0)	-1.0 (3.0)
mPAP (mmHg)	-2.0 (4.0)	-1.0 (3.0)	0.0 (3.0)	-2.0 (3.0) <sup>1</sup>
CI (L/min per square metre)	0.1 (0.6)	0.0 (0.7)	0.6 (0.9)	-0.1 (0.4)
iPVR	-30.6 (130.9)	-51.7 (165.2)	-9.4 (103.1)	0.0 (91.2)

<sup>1</sup>No hemodynamic variation reached statistical significance ( $P > 0.1$  for any value) except for the median mPAP variations in the Milrinone + NO group ( $P = 0.47$ ). MAP: Mean arterial pressure; HR: Heart rate; CVP: Central venous pressure; PAOP: Pulmonary artery occlusion pressure; mPAP: Mean pulmonary arterial pressure; CI: Cardiac index; iPVR: Indexed pulmonary vascular resistance; iNO: Inhaled nitric oxide.

cations were observed. The milrinone concentrations of all samples were very low (average 8.68 ng/mL) and two samples showed a level below the lower limit of quantification (1.25 ng/mL).

## DISCUSSION

In this pilot study, we demonstrated that it is feasible and safe to administer inhaled milrinone and the combination of inhaled milrinone and iNO to patients with moderate to severe ARDS over a short period of time. However, inhaled milrinone had no significant effects on oxygenation and hemodynamic parameters in these patients.

These results are surprising given the beneficial effects of inhaled milrinone in other patient population such as cardiac surgery. Trying to understand these discrepancies, we hypothesized that systemic recirculation of absorbed milrinone and therefore increase pulmonary shunt could potentially explain the lack of oxygenation improvement, though then we should expect pulmonary arterial pressure fluctuations. However, low milrinone plasmatic levels suggest underdosing rather than recirculation. Physiological changes in ARDS may also counteract milrinone effect in such patient populations<sup>[12]</sup>. The dosing itself or inadequacy of our nebulising technique might be related to the relative inefficacy of milrinone.

Our study has many limitations such as the small sample size and a monocentric design. Given the half-life of milrinone it would have been impossible to begin with milrinone and certify lack of residual effect potentially inducing bias in our results including studying use of the combination of milrinone and epoprostenol. The deposition and absorption of nebulized drugs is very variable in mechanically ventilated patients, it would have been interesting to generate a dose-response curve for each drug and then to study the safety of the lowest dose of each drug that gave the maximal response.

In summary, it appeared safe to administrate inhaled milrinone and a combination of inhaled milrinone and iNO to ARDS patients over a short period of time. When comparing the effects of the three inhaled vasodilators (NO, milrinone and epoprostenol), inhaled NO was the only medication significantly improving gas exchanges. Inhaled milrinone appeared safe but failed to improve

oxygenation in ARDS. Further studies are needed in order to confirm usefulness of inhaled milrinone in ARDS and its appropriate administration regimen and nebulising technique.

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## COMMENTS

### Background

Treatment of severe hypoxemia has remained one of the greatest challenges in the intensive care units. Inhaled therapies such as inhaled nitric oxide allow for selective vasodilation of ventilated units, transforming relative dead space into adequate ventilation-perfusion units. The phosphodiesterase type III inhibitor milrinone is a potent pulmonary vasodilator may be a potential alternative to actual costly treatment strategies. Animal studies have suggested a response to milrinone in acute lung injury.

### Research frontiers

Despite several advances in mechanical ventilation, acute respiratory distress syndrome remains a condition with high mortality. New therapies to improve oxygenation and outcomes need to be investigated.

### Innovations and breakthroughs

To their knowledge, this is the first study testing inhaled milrinone as a therapy in acute respiratory distress syndrome and comparing it to more frequently used inhaled therapies. It shows that inhaled milrinone is safe but is not efficacious.

### Applications

Inhaled milrinone was shown to be safe in acute respiratory distress syndrome in our study. Although not efficacious in our trial, it could be further studied in a larger study or with more selected populations to see if an effect can be found.

### Terminology

Milrinone: A phosphodiesterase type III inhibitor that is a potent pulmonary vasodilator that has been used with success as an inhaled therapy for pulmonary hypertension in cardiac surgery.

### Peer-review

This is a case of Acute Respiratory Distress Syndrome, with both methodologically and therapeutically impeccable evolution, as it can be seen in its radiographic progression. The semiotic paradigm is one of the canonical forms of scientific thought that allows to authorize the progression of medical knowledge from particular deductions to general applications. It must be considered the above distinction for this work and its useful effectiveness proposed by their authors.



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