Prospective Study

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

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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 (PaO₂) were recorded before and after each inhaled therapy.
adminstration.

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, inhalated milrinone and the combination of inhalated milrinone and iNO had no impact on systemic hemodynamics. No significant adverse events related to study medications were observed. The median increase of PaO2 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, inhalated milrinone, and iNO added to milrinone. Only iNO and the combination of inhalated milrinone and iNO had a statistically significant effect on PaO2.

CONCLUSION
When comparing the effects of inhaliliated 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 inhalated milrinone as a therapy in acute respiratory distress syndrome and comparing it to more frequently used inhalated therapies. It shows that inhalated 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[1]. 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 vasodilatation of ventilated units, transforming relative dead space into adequate ventilation-perfusion units[1-2]. 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[3-5]. Inhaled prostacyclin has also been used in ARDS and has been shown to significantly reduce pulmonary artery pressure and increase oxygenation[6-9]. However, prostacyclin administration is technically challenging given its short half-life and susceptibility to photo-degradation[10]. The phosphodiesterase type III inhibitor milrinone is a potent pulmonary vasodilator that has been used with success as an inhalated therapy for pulmonary hypertension in cardiac surgery and may be a potential alternative to actual treatment strategies[6-9]. Animal studies have suggested a response to milrinone in acute lung injury[10].

The primary objective of this study was to assess the tolerability and safety of inhalated milrinone in ARDS patients. The secondary objectives included: Evaluation of the efficacy of inhalated milrinone in improving hypoxemia compared to baseline; comparison of the effects of inhalated milrinone, iNO and inhalated epoprostenol in improving hypoxemia and secondary pulmonary hypertension compared to baseline; evaluation of the efficacy of combining inhalated 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 (PaO2) to the fraction of inspired oxygen (FiO2) ≥ 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 nebulisation 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)**

| Parameter | Value (IQR) |
|-----------|-------------|
| 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) |
| PaO2 (mmHg) | 80 (IQR = 39) |
| FiO2 (%) | 80 (IQR = 30) |
| PaO2/FiO2 | 138 (IQR = 68) |
| PEEP (cm H2O) | 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.

Table 1 shows the baseline characteristics of the patients. The median age was 57 years, with a range of 22 years. The gender distribution was 12 men and 3 women. The median SOFA score at ICU admission was 7.5, with an interquartile range (IQR) of 7. The APACHE-Ⅱ score at ICU admission was 23 (IQR = 7). The median PaO2 was 80 mmHg (IQR = 39). The median PaO2/FiO2 ratio was 138 (IQR = 68). The median PEEP was 10 cm H2O (IQR = 2). The median MAP was 75 mm Hg (IQR = 16). The median mPAP was 28 mm Hg (IQR = 7). The median cardiac index was 3.7 L/min per square metre (IQR = 2.6).

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 PaO2 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 PaO2 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-
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 populations 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.

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 vasodilatation 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 it usefulness effectiveness proposed by their authors.

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**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) |
| 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)| -1.0 (4.0)    | -1.0 (3.0)  | 0.0 (3.0) | -2.0 (3.0) |
| 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) |

\(1^{st}\)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.
REFERENCES

1 Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993; 328: 399-405 [PMID: 8357359 DOI: 10.1056/NEJM199302113280605]

2 Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; 353: 2683-2695 [PMID: 16371634 DOI: 10.1056/NEJMra051884]

3 Afshari A, Brok J, Møller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. *Anesth Analg* 2011; 112: 1411-1421 [PMID: 21372277 DOI: 10.1213/ANE.0b013e31820b185]

4 Pappert D, Busch T, Gerlach H, Lewandowski K, Radermacher P, Rossaint R. Aerosolized prostacyclin versus inhaled nitric oxide in children with severe acute respiratory distress syndrome. *Anesthesiology* 1995; 82: 1507-1511 [PMID: 7793662]

5 Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, Seeger W. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; 153: 991-996 [PMID: 8630585 DOI: 10.1164/ajrccm.153.3.8630585]

6 Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, Briegel J, Welte M, Peter K. Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; 154: 1671-1677 [PMID: 8970353 DOI: 10.1164/ajrccm.154.6.8970353]

7 Lowson SM. Inhaled alternatives to nitric oxide. *Anesthesiology* 2002; 96: 1504-1513 [PMID: 12170067]

8 Haraldsson s A, 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: 1439-1445, table of contents [PMID: 11726420]

9 Sablotzki A, Starzmann W, Scheubel R, Grond S, Czeslick EG. Selective pulmonary vasodilation with inhaled aerosolized milrinone in heart transplant candidates. *Can J Anaesth* 2005; 52: 1076-1082 [PMID: 16326679 DOI: 10.1007/BF03021608]

10 Bueltmann M, Kong X, Mertens M, Yin N, Yin J, Liu Z, Koster A, Kappe H, Kuebler WM. Inhaled milrinone attenuates experimental acute lung injury. *Intensive Care Med* 2009; 35: 171-178 [PMID: 18972099 DOI: 10.1007/s00134-008-1344-9]

11 Nguyen AQ, Théorêt Y, Chen C, Denault A, Varin F. High performance liquid chromatography using UV detection for the quantification of milrinone in plasma: improved sensitivity for inhalation. *J Chromatogr B Analyt Technol Biomed Life Sci* 2009; 877: 657-660 [PMID: 19201666 DOI: 10.1016/j.jchromb.2009.01.024]

12 Cepkova M, Matthay MA. Pharmacotherapy of acute lung injury and the acute respiratory distress syndrome. *J Intensive Care Med* 2006; 21: 119-143 [PMID: 16672636 DOI: 10.1177/088506606287045]

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