



Research Article

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# Role of Milrinone on Oxygen Index in Babies Ventilated for Meconium Aspiration Syndrome



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## Abstract

**Background:** Meconium aspiration syndrome (MAS) is a common problem that most paediatricians will encounter in the delivery room and normal newborn nursery. The aim this study was to evaluate the role of Milrinone on oxygen index in babies ventilated for MAS.

**Material and Methods:** This randomized controlled study was carried on 30 babies admitted in NICU with MAS within 24 hours of life on ventilator with Oxygen index  $\geq 8$ . Patients were randomized by serially numbered opaque sealed envelope (SNOSE) method either to undergo milrinone via slow iv infusion pump along with standard management or to receive standard management of MAS in 1:1 equal allocation ratio. Milrinone was given for a maximum of 48 hours and the efficacy of the same was studied in terms of improvement in ventilator parameter i.e. Oxygen index (OI).

**Results:** There was no statistically significant improvement of OI in the milrinone group at 0, 12, 24, 48 hours when compared to the control group with  $p=0.9$ ,  $p=0.96$ ,  $p=0.9$ ,  $p=0.78$  at 0, 12, 24, 48 hours respectively. Mean duration of mechanical ventilation, was more in milrinone group compared to the control group (3.89v/s 3.33) with  $p$  value of 0.9. Mortality during the hospital stay was noticed to be lesser in milrinone group compared to non-milrinone group. There were no complications in any of the babies associated with administration of milrinone.

**Conclusion:** Milrinone didn't prove to be effective in improving oxygen index in babies ventilated for MAS. Babies on milrinone didn't show any improvement in duration of respiratory support. Mortality during the hospital stay was lesser in milrinone group.

## Introduction

Meconium aspiration syndrome (MAS) is a common problem that most pediatricians will encounter in the delivery room and normal newborn nursery. The overall frequency of MSAF varies between 5% to 25% and usually occurs in term or post-term infants [1]. Meconium aspiration syndrome remains one of the most common causes of neonatal respiratory distress [2]. Meconium stained amniotic fluid, as a result of passage of fetal colonic contents into the amniotic cavity, is noted in approximately 12% of all deliveries. Meconium aspiration syndrome (MAS) is noted in 5 % of these infants, 30% of them require mechanical ventilation, more than 4% of MAS infants die accounting for 2 % of all perinatal deaths [3,4]. In utero, meconium passage rarely occurs before 32 weeks of gestation and most babies with meconium stained amniotic fluid are 37 weeks or older [5]. Usually, but not invariably, fetal distress and hypoxia occur before the passage of meconium

into amniotic fluid. These infants are meconium stained and may be depressed and require resuscitation at birth [6].

According to working definitions of the National Neonatal-Perinatal Database of India: MAS should be diagnosed if any two of the following three criteria are present:

- A.Meconium staining of liquor or staining of nails or umbilical cord or skin.
- B.Respiratory distress soon after birth, within one hour of birth.
- C.Radiological evidence of aspiration pneumonitis (atelectasis) and/or Hyperinflation [7].

Acute or chronic hypoxia and/or infection can result in the passage of meconium in utero. In this setting, gasping by the fetus

or newly born infant can cause aspiration of the amniotic fluid contaminated by the Meconium [8]. Meconium aspiration before or during birth can obstruct airways, interfere with gas exchange, decreases lung compliance, causing alveolar oedema, chemical pneumonitis, and pulmonary hypertension<sup>9</sup>. Clinical studies show that pulmonary artery hypertension is always associated in the pathogenesis of severe neonatal MAS which often results in fatal complications. This is generally attributed to increased resistance of a normal pulmonary vascular bed in response to perinatal hypoxia and acidosis [9,10]. Many trials have shown significant improvement in oxygen index with administration of Milrinone. The aim of this study was to know the effect on oxygen index after administration of milrinone in hypoxic babies ventilated for MAS.

## Objective of the Study

**Primary Objective:** To study the effect of Milrinone on oxygen index in babies ventilated for MAS.

### Secondary objectives:

- To study the duration of respiratory support in babies with milrinone and without milrinone
- To compare the mortality rate between MAS ventilated babies with and without milrinone.

## Materials and Methods

The study was a randomized controlled study conducted in the NICU of JSS Hospital Mysore during the study period - May 2011 to September 2013.

**Source of data:** Neonates admitted in NICU with Meconium aspiration syndrome on ventilator with oxygen index of  $\geq 8$  [11] were included. After fulfilling the criteria, patients were randomized by a serially numbered opaque sealed envelope (SNOSE) method either to undergo milrinone via slow IV infusion pump along with standard management or to receive standard management of MAS in 1:1 equal allocation ratio.

**PALS guidelines 2011:** Loading dose of 50 microgram/kg administered over 10-60 followed by continuous infusion over of 0.25-0.75microgram/kg/minute.

**Group A (Study group):** These neonates were given milrinone via slow IV infusion pump along with standard management. Milrinone was given for a maximum of 48 hours.

**Group B (Control group):** These neonates were given standard management of MAS.

In both groups, babies were continuously monitored and blood gases done at 0, 12, 24 and 48 hours after initiating treatment.

$$OI = FiO_2 \times MAP \times 100 / PaO_2$$

## Method of collection of data

### Inclusion Criteria

Term neonates with Meconium aspiration syndrome requiring ventilator support with oxygen index of  $\geq 8$  within 24 hours of life.

### Exclusion Criteria

- Babies with respiratory distress syndrome other than MAS are excluded
- Babies with MAS referred from other hospitals after 24 hours of age.
- Babies having surgical problems needing immediate surgical interventions
- Babies with acute renal failure.

### Ventilation Criteria

- Baby born with meconium aspiration with poor respiratory efforts.
- Baby born with meconium aspiration with severe respiratory distress requiring  $PaO_2 > 40\%$  to maintain saturation above 93%.
- Baby born with meconium aspiration with blood gas showing hypoxemia and hypercarbia with acidosis (either respiratory or metabolic).

## Parameters to be studied

**Primary outcome:** Difference in oxygen index after 0hr, 12hr, 24hr, and 48hr in both groups.

### Secondary outcome:

- Difference in duration of respiratory support in both groups.
- Difference in the mortality rate in both the groups.

## Statistical methods

Descriptive statistics is done measuring mean, median and standard deviation. Inferential statistics is done by using Mann Whitney test (to compare median of two independent groups), chi-square test (to compare independent proportions). P value  $< 0.05$  is considered as statistically significant. All statistical calculations are done using SPSS version 13.0. Graphical presentation was done by using Microsoft Excel.

## Results

Mean OI at admission is 13.72 v/s 12.99  $p=0.9$  no statistical significant difference at 12hrs OI=8.97 V/S 8.80  $p=0.96$ , at 24hrs OI=6.73 V/S 6.34  $p=0.96$ , at 48hrs OI=5.59 V/S 4.85  $p=0.78$  which has statistically no difference in each session or duration in the OI of both the group. No differential decrease in the OI in the case group compared to the control group. Mean ventilator days =3.89 v/s 3.33 with no statistical difference in the birth weight of cases and controls as the p value is 0.9. Mean Oxygen days =2.8 v/s 1.67 with no statistical difference in the birth weight of cases and controls as the p value is 0.65.

Mean total respiratory support (Oxygen days+ ventilator days) =6.67 v/s 5 with no statistical difference in the total respiratory support and controls as the p value is 0.74. Mortality during the hospital stay was noticed to be lesser in milrinone group (One)

compared to non-milrinone group (Three). One baby died due to ventilator associated pneumonia with sepsis (milrinone group). In non milrinone group, 3 babies died with sepsis/DIC/Pulmonary hemorrhage. There was no complication in any of the babies associated with administration of milrinone (Figure 1).

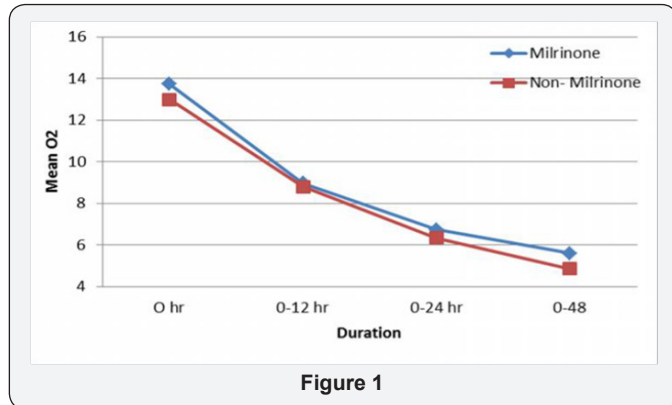


Figure 1

## Discussion

Milrinone is a selective phosphodiesterase inhibitor which has positive inotropic, vasodilator action and mild chronotropic action [11-23]. Used as an adjunct to nitric oxide in patients with persistent pulmonary hypertension of newborn, low cardiac output (especially after cardiac surgery) [24] and in septic shock [25]. There is some evidence for its use in preventing low cardiac output in patients undergoing cardiac surgery. It is for short term treatment only and should generally not be used for longer than 72 hours [12,21].

It acts on pulmonary vasculature by decreasing systemic vascular resistance, increasing cardiac contractility and cardiac output [26]. By reducing pulmonary after load, improving RV compliance and increasing myocardial contractility, milrinone improves passive left ventricular filling hence increased cardiac output and blood pressure stability [27].

Milrinone is a bipyridine compound that selectively inhibits PDE III. In a pediatric rodent model of hypoxia-induced pulmonary hypertension, the expression of PDE IIIa is up-regulated, and pulmonary artery relaxation is increased with milrinone treatment [28]. Experience with this drug in neonates is limited. Early studies of milrinone suggested that it was a relatively ineffective inotrope in a neonatal rabbit experimental model [29] and speculated that postnatal maturation of affinity occurred; however, in neonatal canine and porcine models, positive inotropy was demonstrated in the neonatal heart [30,31].

We identified only few studies that quantified for this review.

## First Cochrane Neonatal Review

The objective of study was to compare, assess efficacy and safety in infants with PPHN either treated with: milrinone compared with placebo or no treatment; milrinone compared with iNO; milrinone as an adjunct to iNO compared with iNO alone; milrinone compared with potential treatments for PPHN

other than iNO. The author conclusion is the efficacy and safety of milrinone in the treatment of PPHN are not known and its use should be restricted within the context of RCTs. In our study also Milrinone didn't prove to be effective in improving oxygen index in babies ventilated for MAS (PPHN a known complication) [32].

Second Pilot studies:

A. Bassler on 4 neonates revealed improvement in oxygen index. However out of 4 babies 2 develop severe IVH and one small IVH [33].

B. Another study done in Korea by Doo-Kyo In, M.D SungWan Yang et al on 6 neonates revealed Milrinone proved to be effective in improving oxygen index [34].

C. McNamara PJ et al on nine full term neonates also revealed early improvements in oxygen index with milrinone [35].

There were no complications in babies in the last two pilot studies associated with the administration of milrinone. Currently a study on pharmacokinetic data of milrinone of infants with PPHN are currently collected (kirplani) [36].

## Conclusion

A. Milrinone didn't prove to be effective in improving oxygen index in babies ventilated for Meconium Aspiration syndrome compared to non-milrinone group.

B. Babies on milrinone didn't show any improvement in duration of respiratory support.

C. Mortality during the hospital stay was lesser in milrinone group.

1) Serial ECHO evaluation for pulmonary hypertension couldn't be done to know the effect of milrinone on pulmonary pressure.

2) Long term morbidity couldn't be determined.

3) Study needs to be done on large number of sample size.

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