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Effect of Excessive Fio2 on Oxygenation and Pulmonary Outcome in Mechanically Ventilated Young Infants; a Prospective Study

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Abstract
Background: *Optimal titration of inspired oxygen is important to prevent hyperoxia in mechanically ventilated patients in ICUs, but there is paucity of data about FiO_2 practice among patients in NICUs. We evaluate the association of excessive FiO_2 exposure with acute lung injury in mechanically ventilated young infants.*
Methods: *By prospective study, we enrolled NICU patients who underwent invasive mechanical ventilation. Ventilator settings (FiO_2) and corresponding SpO_2 were collected for the first 48 hours. Excessive FiO_2 was defined as $FiO_2 > 0.7$. The association between excessive exposure and pulmonary outcomes was analyzed by change in oxygenation index (OI) and lung injury score by correlation.*
Results: *Of 40 patients who met the inclusion criteria, 30 (75%) were exposed to excessive FiO_2 but no significant differences irrespective of excessive FiO_2 implementation ($p=0.67$), except improvement of SpO_2 in both group (76.7% vs 70%). There was negligible correlation between FiO_2 and change of PaO_2 ($r =0.036$). Change of SpO_2 and OI had positive association with FiO_2 ($r =0.01$ and 1 respectively). 20% patient developed ALI & 50% ARDS instead of 10% ALI & 27% ARDS with high FiO_2 among ventilated patients.*
Conclusions: *Excessive oxygen supplementation improves SpO_2 but causes ALI /ARDS in mechanically ventilated patients.*
Keywords: *Acute lung injury, FiO_2, Hyperoxia , Mechanical ventilation.*

I. Introduction

Oxygen is now considered as an important drug required for the management of hypoxaemia and several diseases due to hypoxic conditions. It is one of the most critical considerations in management of diseases but remains poorly understood and inadequately practiced; frequently administered on verbal orders.[1,2] Hypoxia and hyperoxia both produce detrimental effects at a cellular level.[3] Healthcare practitioners are well aware of the catastrophic effects of hypoxia, and this has led to the "more is better" culture of oxygen supplementation.

Adverse effects of hyperoxia in healthy adults have been documented since the 1940s.[3,4] For support of respiratory system two basic tools are available: supplemental oxygen and mechanical ventilation. Supplemental oxygen raises the alveolar PO_2, in turn, for given alveolar-arterial oxygen difference, raises PaO_2. Unfortunately, while these approaches can help tissue oxygenation, they have substantial toxicities that can cause patient harm (iatrogenic injury). High FiO_2 can cause a variety of injuries that was increasingly apparent over last several decades.[5] Prolonged high FiO_2 in patients requiring mechanical ventilation worsens gas exchange by producing free radicals and causes oxygen injury in lungs, decreases ciliary efficacy, and produces hyperoxic bronchitis and atelectasis.[3,6]

Persistent hypoxia, despite adequate oxygen therapy, is common in patients suffering from acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).[7] ALI presents initially with hyperemia, which lead to mechanical ventilation with high FiO_2. If oxygen is continually supplemented without titration, it may inadvertently perpetuate ALI.[3] Factors results in ventilator induced lung injury, may further worsen the pre-existing ALI/ARDS.[7]

This has led to rethinking of the targets for blood oxygenation and tissue oxygen delivery, titration of supplemental oxygen which is important, but not adequately practiced. This paper will focus on injuries that can occur during oxygenation support by mechanical ventilation and evaluate the association of excessive FiO_2 & pulmonary outcome to reexamine the future goals for oxygenation.

II. Material And Methods

A prospective observational study was designed to evaluate relationship between NICU care practices and the occurrence of lung injury among them who underwent invasive conventional mechanical ventilation for 24 to 48 hours from 1st June, 2013 to 31st July, 2014. The enrolled patients who were admitted in NICU on mechanical ventilation at any point of time period and corrected age at start of ventilation was not older than 59

days. Exclusion criteria included bronchopulmonary dysplasia, paralyzed hemidiaphragm, surgery for heart or lung pathology and congenital anomalies in heart & lungs. A previously validated surveillance tool (ALI Sniffer) was an excellent screening tool, used for all patients where a negative predictive value ranging from 98-100%, and sensitivity of 96% (95%, CI 94-98%). The criteria for identification of the patients by the ALI Sniffer were arterial blood gas analysis: PaO_2/FiO_2<200 mmHg for ARDS and <300 mmHg for ALI (In case of multiple arterial blood gas values, the worst value during the 24 hour was selected), chest radiograph: edema or bilateral infiltration and invasive mechanical ventilation for acute respiratory failure or duration >12 hours within a single 24-hour period.[3]

Mechanical ventilation setting depends on our institution protocol. Oxygenation goals are not part of the protocol and practiced at the discretion of bedside clinicians. Demographic data (gestational age, birth weight, sex, age at the start of ventilation) were recorded for each patient. Several clinical information and laboratory parameters (bedside evaluation of respiratory rate, heart rate, apnoea, cyanosis, grunting, chest indrawing, hemoglobin and pulse oximetry) of each infant's were also assessed before received ventilator support. We collected data about the ventilator settings, fraction of inspired oxygen (FiO_2), blood gas data and oximetry values from bedside. The data were analyzed for all included patients, but also subgroups according to excessive FiO_2. Excessive FiO_2 was defined as FiO_2 > 0.7-1.0. Data were presented as mean with standard deviation, percentage and compared by using chi-square and independent sample test. The association between excessive exposure and pulmonary outcomes was assessed by change in oxygenation index and oxygen toxicity (by FiO_2, PaO_2 and lung injury score) within first 48 hours of exposure and was analyzed by correlation. Two-tailed p values (<0.05) were used to indicate statistical significance. All analyses were conducted with SPSS version 21.

III. Results

40 patients met the inclusion criteria who were on mechanical ventilation after blood gas analysis and measured SpO_2. The nadir hemoglobin was similar in both groups (13.09 vs 13.83 g/dl, p=0.59) (table1). SpO_2 before ventilation was also similar (59.47 vs 66.70%, p=0.81) (table 1). Use of sedation in both groups was as per the pre-designed ICU protocol. Irrespective of initial SpO_2, excessive FiO_2 (0.7-1.0) exposure was found in 30(75%) patients and baseline characteristics, lung injury scores, risk factors for ALI/ARDS were similar between patients with or without excessi

Table 1. Baseline Variables

P value	No excessive FiO_2 (n =10)	Excessive FiO_2 (n= 30)		
0.18	1898 ± 741.8	2335.03 ± 596.99	Wt (mean ± SD)	
0.1	9.1 ± 14.8	9 ± 7.5	original age(mean ± SD)	
0.35	42 ± 28.26	40.33 ± 22.57	Respiratory rate (mean ± SD)	
0.99	95.84 ± 1.34	97.83 ± 1.25	Temperature(mean ± SD)	
0.81	66.70 ± 28.22	59.47 ± 26.11	SPO_2 (mean ± SD)	
0.59	13.83 ± 3.07	13.09 ± 2.59	Hb(gm/dl) (mean ± SD)	
0.14	8 (80%)	16 (53.3%)	Sex, male	
0.6	4 (40%)	16 (53.3)	term	Gestation
	6 (60%)	13 (43.3%)	preterm	
0.7	4 (40%)	9 (30%)	Need of resuscitation after birth	
0.06	4 (40%)	22 (73.3%)	Severe chest indrawing	
0.25	5 (50%)	9 (30%)	Apnoea	
0.27	3 (30%)	15 (50%)	Grunting	
0.95	8 (80%)	24 (80%)	cyanosis	
0.85	6 (60%)	17 (56.7%)	Capillary refill time delayed	
0.26	2 (20%)	7 (23.3%)	Sepsis	
0.26	1 (10%)	6 (20%)	pneumonia	

The initial FiO_2, PIP, Ventilator Rate & MAP at the onset of mechanical ventilation were similar in both groups and after ventilation PaO_2/ FiO_2 were significantly differ in both groups by statistical analysis (145.17 vs 328.40, p=0.013)(table 2). After ventilation, there was significant improvement of SpO_2 in both group (76.7% vs 70%) but no significant differences irrespective of excessive FiO_2 implementation (p=0.67)(table 2). Both groups had similar PaO_2 values at beginning (102.96 vs 105.23, p=0.08), significantly improved after ventilation (103.23 vs 136.54, p=0.013) but statistically no difference between two groups.

Table 2. Mechanical Ventilation Related Variables

P value	No excessive FiO_2 (n =10) Mean ± SD	Excessive FiO_2 (n= 30) Mean ± SD	
0.45	52.4 ± 7.37	94 ± 9.04	FiO_2
0.96	20.1 ± 3.21	19.7 ± 2.96	PIP
0.001	4.4 ± 0.52	4.1 ±0.30	PEEP
0.725	43.4 ±8.78	37.07 ± 7.89	Ventilator rate
0.23	267 ± 178.4	261.82 ± 330	PaO_2/ FiO_2, before ventilation
0.013	328.40 ± 161.83	145.17 ± 80.09	PaO_2/ FiO_2, after ventilation
0.11	10.01 ± 1.63	8.87 ± 1.26	MAP
0.67	7(70%)	23(76.7%)	Spo2>90%

Table 3. Difference of PaO_2 before and after ventilation

P value	No excessive FiO_2 (n =10) Mean ± SD	Excessive FiO_2 (n= 30) Mean ± SD	
0.08	105.23 ± 58.88	102.96 ± 91.95	PaO_2 before ventilation
0.52	146.47 ± 80.92	133.23 ± 66.24	PaO_2 after ventilation

In our result, there was negligible correlation between FiO_2 and change of PaO_2 after ventilation (r=0.036). So, improvement of oxygenation was not depending on excessive FiO_2, other parameters like PIP, PEER, Ti also were responsible for oxygenation. Change of SpO_2 and OI had positive association with FiO_2(r=0.01 and 1 respectively) (Figure 2 & 3).

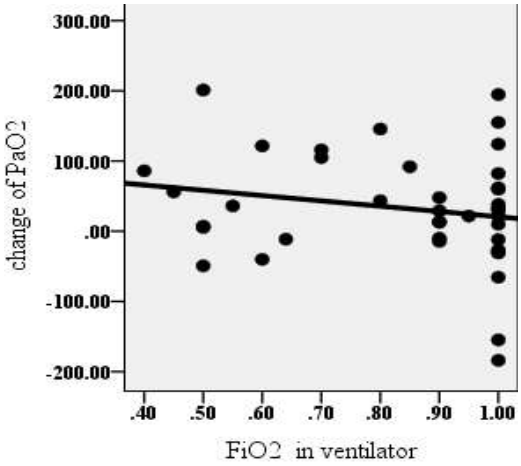


Fig-1: Relation between FiO_2 and Change of PaO_2 (Before & after ventilation)

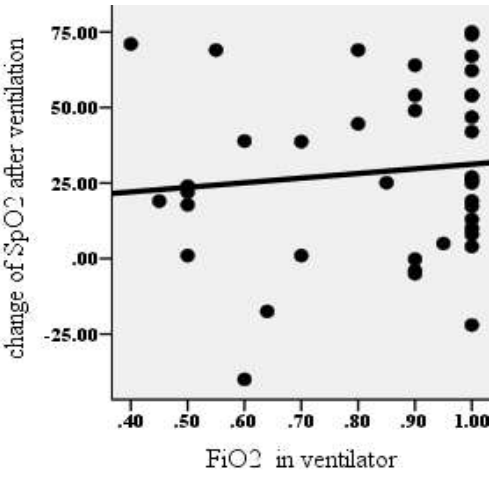


Fig-2: Relation between FiO_2 and Change of SpO_2 (Before & after ventilation)

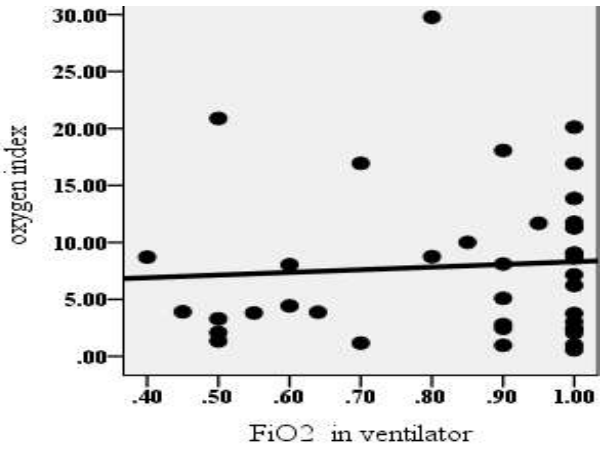
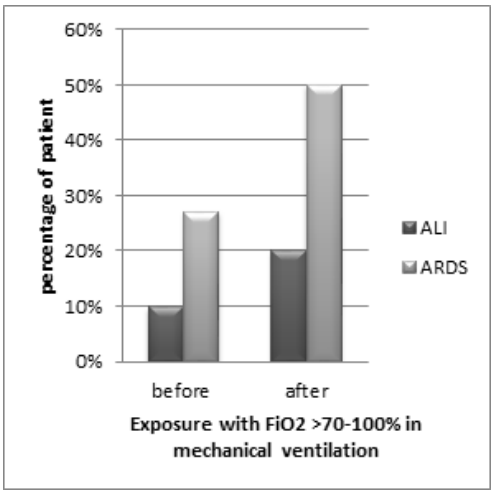


Fig-3: Relation between FiO_2 and Oxygen index (OI)

Before ventilation according to ALI Sniffer, 10% patients were suffering from ALI & 27% from ARDS. After high exposure of FiO_2 (>0.7-1), 20% patient developed ALI & 50% ARDS in comparison to low exposure group (FiO_2 <0.7) where only 10% patient developed ARDS after ventilation and there was no change in ALI incidence (Figure 4).



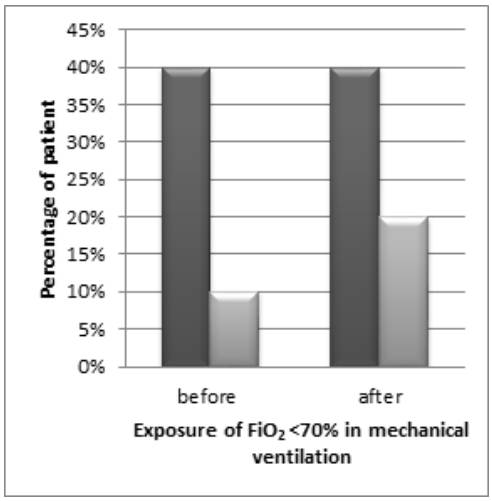


Fig-4(a, b): Distribution of Lung injury pattern after exposure of mechanical ventilation with **Fio2 >0.7-1 and FiO2<0.7**

IV. Discussion

There are three types of risks associated with long term use of oxygen: physical, functional, cytotoxic which are higher particularly with FiO_2 over 50%.[1] Non-human primates develop lung injury in 1-2 days when exposed to FiO_2 of 1.0, but this injury may take up to 2 weeks to when FiO_2 of 0.6.[5] Importantly, the presence of various disease states and inflammatory processes may modulate the response to oxygen toxicity in lung. Most consensus groups have argued that FiO_2 values <0.4 are safe for prolonged periods of time and FiO_2 values of >0.8 should be avoided if at all possible.[5]

This is not a well-studied area, but there is evidence in the cardiology literature that routine use of supplemental O_2 in patients with acute myocardial infarction, not hypoxemic may worsen outcomes.[5,8] Several recent reports have noted that hospitalized patients with supplemental oxygen results unnecessarily high level of PaO_2 (generally above 120 mmHg) and actually have a worsening of clinical outcomes.[5,9] With proper compensatory mechanisms, human life can thrive with lower PaO_2 than traditional clinical thresholds (55-60mm Hg).[5]

Traditional oxygenation support targets have focused on monitoring arterial PaO_2, arterial O_2 content and cardiac output. Commonly recommended targets have been an arterial PaO_2 >55mm Hg, hemoglobin levels of at least 7 g/dl (but perhaps as high as 9-10 g/dl in high O_2 demand states) and cardiac indices above 2L/min/m^2. These targets will keep O_2 delivery near normal.[5,9] It is thus important to look at the relative benefits and risks of each of these used manipulations. A PaO_2 increasing from 45 to 68 mm Hg (50% increase) results in 22% increase in O_2 delivery; a PaO_2 rising from 68 to 124 mmHg (82% increase) results in O_2 delivery increased only 9%. [5]

According to Linda J et al, maximum FiO_2 of 1.0 were associated with 1.8 times risk of CLD than lower PIP and FiO_2 group.[11] Our data support this hypothesis and provide evidence that excessive FiO_2 in respiratory management might be associated with oxygen toxicity (lung injury). High FiO_2 impair surfactant synthesis, exhaust the antioxidant defenses, and cause direct cellular injury to the immature lung. Several previous studies[11,12] revealed association between high inspired oxygen and lung injury (CLD).[11] In our analysis, inspired oxygen concentrations were higher among young infants (75%). Evaluating specific ventilator setting and blood gas data during ventilation PIP (18- 24 cm of H_2O) and FiO_2 (0.7-1.0) were associated with increased ALI risk. Thus our findings are inconsistent with those previous investigators, who reported increased ALI risk among infant with excessive FiO_2 values.[3]

Oxygen may contribute alteration in immature lung structure after ventilation-induced lung injury. Exposure to hyperoxia (100% O_2) further increased both elastin deposition and myofibroblast differentiation, compared with 21% O_2 and ventilation with oxygen increased cellular apoptosis in the distal lung parenchyma.[13] The incidence of ARDS has been reported to be 43% in sepsis,[7,14] In our study, the rate was only 23% in excessive FiO_2 group. A combination of high FiO_2 and previously injured lung result in ventilator induced lung injury, which may further worsen the pre-existing ALI/ARDS.[7] In ALI/ARDS, activated inflammatory cells such as macrophages and neutrophils produce many reactive oxygen intermediates in presence of high PaO_2.

Glutathione, a natural cellular antioxidant, is rapidly depleted in ALI along with diminished plasma level of vitamin E & C.[7] Patients who developed either ALI or ARDS had higher mortality rates than those who did not develop lung injury (25% ALI; 45.5% ARDS; 10.3% no ALI/ARDS; $p<0.001$).[15]
Our study has several limitations. Enrolment was limited, local practice patterns may limit the generalizability of these results. We enrolled patients over only one year period.

V. Conclusions

Excessive oxygen supplementation improves SpO_2 but causes ALI /ARDS in mechanically ventilated patients.

VI. Recommendation

In order to reduce iatrogenic harm, clinicians could be comfortable with maintain lower levels of PaO_2 60-80 mm Hg to rationalize treatment of oxygen therapy (FiO_2) and achieve the maximum benefits. Further studies in larger series are needed to confirm these findings.

Declarations

Conflict of interest*: The authors declare that they have no conflict of interest.*
Ethical approval: *The ethical Review Committee of BICH, Dhaka Shishu Hospital approved the study.*

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