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Effect of Conventional High Flow Oxygen Therapy Compared to Conservative Oxygen Therapy in Mechanically Ventilated Neonates

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Abstract

Background: *Mechanically ventilated neonates are usually exposed to high oxygen therapy and due to common clinical practice and lack of knowledge about the target and optimum dose & duration of oxygen administration hyperoxia occurs frequently. The study was done to compare the effect between conventional high flow and conservative oxygen therapy.*

Materials & Methods: *A prospective study was done in Dhaka Shishu Hospital NICU from July 2013 to June 2014 and enrolled those were underwent invasive mechanical ventilation. Ventilator settings, FiO_2 and SpO_2 were recorded for the first 48 hours. The comparison of conventional high FiO_2 (> 0.7-1.0) and conservative FiO_2(< 0.7) therapy was assessed by SpO_2, PaO_2, PaO_2/ FiO_2 ratio and lung injury score within 48 hours of exposure and was analyzed.*

Results: *Among total 40 cases 30/40(75%) were exposed to conventional high FiO_2. After invasive mechanical ventilation, there was improvement of SpO_2 in both group (76.7% vs 70%) but there was no significant difference in between conventional high FiO_2 implementation and conservative group(P=0.67). PaO_2/ FiO_2 ratio also improved after ventilation (145.17 vs 328.40, P=0.013) in both groups but indicate lung injury in conventional high FiO_2 group. After invasive mechanical ventilation 53% (16/30) patients were suffering from acute lung injury(ALI) & acute respiratory distress syndrome (ARDS) with high exposure of FiO_2 (>0.7-1) and only 40% (4/10) patient developed ALI & ARDS in low exposure group (FiO_2<0.7).*

Conclusions: *Conventional high FiO_2 or liberal O_2 therapy in mechanically ventilated neonates improves SpO_2 but conventional high FiO_2 may causes iatrogenic lung injury.*

Key words: *Fraction of inspired oxygen (FiO_2); SpO_2; hyperoxia; mechanical ventilation; Acute lung injury (ALI).*

Introduction

Oxygen is one of the most common therapy in mechanically ventilated patients in all Neonatal Intensive Care Unit around the world.[1] In spite of less awareness regarding adverse effects of hypoxia & hyperoxia, healthcare practitioners have practice high level oxygen supplementation.[2,3] But excess oxygen has toxic effect in various organs. Hyperoxia occurs due to clinical practice of high FiO_2 and lack of knowledge about the target and optimum dose & duration of oxygen administration in ventilated patients.[4] Supplemental increasing FiO_2 is one of the basic tools for respiratory support. Increased FiO_2 raises the alveolar PaO_2 as well as increase alveolar-arterial oxygen deference and improve arterial oxygen (PaO_2).[5] Patients who underwent mechanical ventilation with prolonged high FiO2 result worsens gas exchange, produce free radicals that again causes oxygen induced lung injury, decreases ciliary efficacy, and produces hyperoxic bronchitis and atelectasis.[2,6] Comroe showed oxygen decrease arterial blood pressure in asphyxiated baby and in 1950s, he also warned that a single breath of 100% oxygen with

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uneven alveolar ventilation has adverse effect on respiratory control and mental status.[3] High regional cerebral saturation has an association with peri-intraventicular hemorrhage and blindness reflects as retinopathy of prematurity.[4] Patients suffering from acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) commonly have persistent hypoxia despite of adequate oxygen therapy[7] and need mechanical ventilation & high FiO2.[2] But continuous high oxygen supplementation without titration may inadvertently perpetuate ALI[8] and further worsen the pre-existing ALI/ARDS.[7] Now it should be our consideration that we need to avoid hypoxia as well as hyperoxia in our daily practice. This study focused on effect of conventional high flow oxygen therapy compared to conservative oxygen therapy in mechanically ventilated neonates and it also helps to improve ventilation strategies.

Materials & Methods

The prospective study was conducted in NICU of Dhaka Shishu (Children) Hospital from July 2013 to June 2014. It was approved by institution's Bioethics Committee and was done among the patients who were 0 to 28 days old & admitted in NICU for invasive mechanical ventilation at any point of time during this study period.

Inclusion criteria of infants were who required mechanical ventilation due to apnoea or irregular breathing pattern, in respiratory failure (pH <7.25, $PaCO_2$>55mmHg, PaO_2<50mmHg), failure of nasal CPAP of 7mm of H_2O. Exclusion criteria consists of patients who were less than 48 hours' ventilation & already had lung pathology like bronchopulmonary dysplasia due to ventilator dependency, paralyzed hemidiaphragm, surgery for heart-lung pathology and congenital anomalies in heart and lungs.

Mechanical ventilation setting depends on our institution protocol. Only SpO_2 mentioned as oxygenation goal in this protocol and practiced at the discretion of bedside clinicians. Others like OI, PaO_2/FiO_2 ratio was not included in oxygenation goals.

Demographic data like gestational age, birth weight, sex, age etc. were recorded at the start of ventilation for each patient. Several clinical information (bedside evaluation of respiratory rate, heart rate, apnoea, cyanosis, grunting, and chest indrawing), laboratory parameter (hemoglobin, blood gas analysis) and pulse oximetry of each infant were also assessed before initiation of ventilator support. We collected data about the respiratory support, ventilator settings, fraction of inspired oxygen (FiO_2), blood gas data and oximetry values from bedside recoding forms at the point of starting ventilation, 24 hours & 48 hours of ventilation. The data were analyzed for all included patients, but in subgroups (conventional and conservative), according to high or excessive FiO_2 exposure during 1st 48hours of mechanical ventilation. Conventional high FiO_2 group was assigned to FiO_2>0.7-1.0 and conservative group used FiO_2<0.7, among these ventilated neonates during this period. Blood gas analyzed in Dhaka Shishu hospital laboratory by RAPIDLAB gas analyzer before ventilation and after 1 hour of ventilation or after 1 hour of any parameter changes according to patient's condition within 1st 48 hours of ventilation. Data are presented as mean with standard deviation and percentage were compared using chi-square. A previously validated surveillance tool (ALI Sniffer) was used to screen all patients for lung injury score. The criteria for identification by the ALI Sniffer were the following: (a) Qualifying arterial blood gas analysis: PaO_2/FiO_2<200mmHg for ARDS and <300mmHg for ALI (In case of multiple arterial blood gas values, the worst value during the 24 hours was selected), (b) Qualifying chest radiograph report: edema or bilateral infiltration & (c) Invasive mechanical ventilation for acute respiratory failure or duration >12 hours. The comparison of conservative and conventional FiO_2 therapy was assessed by SpO_2, partial pressure of oxygen (PaO_2), PaO_2/ FiO_2 ratio and lung injury score within 48 hours of exposure and was analyzed by chi-square test and risk ratio. A P value <.05 was considered significant.

Result

During study period, only 40 patients meet the inclusion criteria. Among them 30(75%) patients were exposed to conventional high FiO_2 (0.7-1.0) and 10 (25%) patients to conservative oxygen therapy means FiO_2<0.7 irrespective of initial SpO_2. Baseline characteristics (weight, sex, gestation, respiratory rate, temperature, chest indrawing, apnoea, grunting, cyanosis & capillary refill time) have no statistical differences among conservative and conventional high FiO_2 exposure groups (table I).

Table-I

Baseline Variables

Characteristics		Conventional high FiO_2 exposure group (n= 30)	Conservative FiO_2 Exposure group (n =10)	P value
Weight (mean ± SD)		2335.03 ± 596.99 gm	1898 ± 741.8 gm	0.18
Original age (mean ± SD)		9 ± 7.5 days	9.1 ± 14.8 days	0.1
Respiratory rate (mean ± SD)		40.33 ± 22.57 br/min	42 ± 28.26 br/min	0.35
Temperature (mean ± SD)		97.83 ± 1.25 p F	95.84 ± 1.34 p F	0.99
SPO_2 (mean ± SD)		59.47 ± 26.11	66.70 ± 28.22	0.81
Hb (gm/dl) (mean ± SD)		13.09 ± 2.59 gm/dl	13.83 ± 3.07 gm/dl	0.59
Sex, male		16 (53.3%)	8 (80%)	0.14
Gestation	Term	16 (53.3)	4 (40%)	0.6
	Preterm	13 (43.3%)	6 (60%)	
Need of resuscitation after birth		9 (30%)	4 (40%)	0.7
Severe chest indrawing		22 (73.3%)	4 (40%)	0.06
Apnoea		9 (30%)	5 (50%)	0.25
Grunting		15 (50%)	3 (30%)	0.27
Cyanosis		24 (80%)	8 (80%)	0.95
Capillary refill time delayed(>3 seconds)		17 (56.7%)	6 (60%)	0.85

The hemoglobin was similar in both groups (13.09 vs 13.83 g/dl, P=0.59) (table I). SpO_2 (59.47 vs 66.70%, P=0.81) before ventilation was also similar in both groups (table I). Use of sedation in both groups were as per the pre-designed protocol for NICU. The initial PIP, Ventilator Rate & MAP at the onset of mechanical ventilation were similar in both groups but PEEP significantly differs in both groups by statistical analysis (PEEP, 4.1 vs 4.4, P=0.001. (Table II).

Both groups had similar PaO_2 values at beginning (102.96 ± 91.95 vs 105.23 ± 58.88, P=0.08), significantly improved after ventilation (133.23 ± 66.24 vs 146.47 ± 80.92, P=0.52) but the improvement was not statistically different between two groups (Table III).

Table II

Mechanical Ventilation Related Variables in two groups

Ventilator parameter	Conventional high FiO_2 exposure group Mean ± SD	Conservative FiO_2 exposure groupMean ± SD	P value
FiO_2	94 ± 5.04	52.4 ± 7.37	0.45
PIP	19.7 ± 2.96	20.1 ± 3.21	0.96
PEEP	4.1 ±0.30	4.4 ± 0.52	0.001*
Ventilator rate	37.07 ± 7.89	43.4 ±8.78	0.725
MAP	8.87 ± 1.26	10.01 ± 1.63	0.11

Table III

Difference of PaO_2 before and after ventilation

	Conventional high FiO_2 exposure group Mean ± SD	Conservative FiO_2 exposure group Mean ± SD	P value
PaO_2 before ventilation	102.96 ± 91.95	105.23 ± 58.88	0.08
PaO_2 after ventilation	133.23 ± 66.24	146.47 ± 80.92	0.52

Table IV

Improvement of tissue oxygenation with oxygen therapy

	Conventional high FiO_2 exposure group Mean ± SD	Conservative FiO_2 exposure group Mean ± SD	P value
SpO_2>90%	23(76.7%)	7(70%)	0.67
PaO_2/ FiO_2, before ventilation	261.82 ± 330	267 ± 178.4	0.23
PaO_2/ FiO_2, after ventilation	145.17 ± 80.09	328.40 ± 161.83	0.013*

Table V

Distribution of Lung injury pattern after exposure of mechanical ventilation with Conventional high FiO_2>70-100% and conservative low FiO_2<70%

Fio2 status	Lung injury after ventilation N(%)	Improved after ventilation N(%)	Risk ratio
Conventional	16 (53%)	14 (47%)	1.7
Consevative	4 (40%)	6 (60%)	

After ventilation with oxygen therapy by increasing FiO_2 values, no statistical change in SpO_2 but PaO_2/ FiO_2 ratio improved significantly after ventilation (145.17 vs 328.40, P=0.013) (Table IV).

After ventilation according to ALI Sniffers lung injury score, 53% (16) patient suffering from lung injury as ALI & ARD with high exposure of FiO_2 (>70- 100%) and only 40% (4) patient developed ALI & ARDS in low exposure group (FiO_2<70%). According to risk ratio calculation lung injury is more probability in conventional High Fio2 exposure group which indicated excessive FiO_2 is harmful for lung condition. (Table V)

Discussion

Higher FiO_2 particularly over 50% may associated with physical, functional, cytotoxic effects like long term use of oxygen.[9] While Non-human primates exposed to FiO_2 values of 1.0 develop clinically lung injury within 1-2 days, it will take up to 2 weeks to develop at a FiO_2 of 0.6.[8] The determinants of oxygen delivery include hemoglobin, cardiac output, and oxygen saturation. Therefore, clinicians may tend to hyper oxygenate in the presence of anemia associated with hemodynamic compromise. Hemoglobin concentration has wide range (7.7-19 gm/dl) which reflect need of excessive FiO_2 to maintain normal level of SpO_2. But this strategy is harmful to immature lungs and causes lung injury. Commonly recommended targets have been an arterial PaO_2 of >55 mm Hg, hemoglobin levels of at least 7 g/dl (but perhaps as high as 9–10 g/dl in high O_2 demand states). These targets will keep O_2 delivery near normal.[8] Less hemoglobin concentration, low cardiac output is the confounding factor for high oxygen demands. Therefore, we excluded cardiac patients and keep hemoglobin level above 10 gm/ dl.

Due to presence of various disease states and inflammatory processes, it is not clear the 'safe' oxygen concentration or duration of exposure is in sick humans which may cause oxygen toxicity in lung. Most consensus groups have argued that FiO2 values <0.4 are safe for prolong periods of time and that FiO_2 values of >0.8 should be avoided in any condition if possible. These are most obvious in the neonates who developed retinopathy of prematurity after exposure to high oxygen concentrations.[8]

Interestingly, several recent reports have noted that hospitalized patients received unnecessarily supplemental oxygen, having high level of PaO_2 (generally above 120 mmHg) and actually have a worsen clinical outcome.[8,10] With proper compensatory mechanisms, human life can thrive with lower PaO_2 than traditional clinical thresholds (55-60mm Hg).[8] Conventional oxygenation support have focused on monitoring SpO_2 rather than arterial PaO_2 because of unavailability of frequent ABG.

In our study PaO_2 is >100 and most of initial FiO_2 started from 1. But the aim of ventilation should be use with maximum FiO_2 for short duration and lowest possible pressure with minimum FiO_2 to maintain oxygenation for longer period.[11] FiO_2 requirement reflects the severity of respiratory failure. FiO2 requirement > 0.6 were found to be significant independent predictors of fatality in mechanically ventilated neonates.[12] Higher SpO_2 target (>95%) is associated with more time spent in hyperoxia and PaO_2 more than 80 mmHg. 91-95% SpO_2 target helps to avoid dangerous hypoxaemia which causes ROP, altered brain development and other pulmonary morbidities associated with hyperoxia. So, FiO_2 should be used at a dose that correct hypoxia and avoid hyperoxia. In our study target SpO_2 is 90-100% which is a wide range and more chance of fluctuation or need of high FiO_2 for long time. Now a days some literature suggests automated FiO_2- SpO_2 control system in neonates who required respiratory support.[4,11,14] SpO_2 target range reduces hyperoxia as well as significant reduction in pulmonary and retinal morbidity.[14]

Commonly recommended targets, an arterial PaO_2>55mm Hg, hemoglobin levels of at least 7 g/dl and cardiac indices above 2L/min/m^2 will keep O_2 delivery near normal.[8,10] 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%.[8] Rising PaO_2 always not beneficial, increase FiO_2 with high PaO_2 may cause oxygen induced lung injury. According to Linda J et al. maximum FiO_2 of 1.0 were associated with 1.8 times risk of chronic lung disease than lower PIP and FiO_2 group. High FiO_2 impair surfactant synthesis, exhaust the antioxidant defenses, and cause direct cellular injury to the immature lung.[15] Our data also support this hypothesis and provide evidence that conventional high FiO_2 in respiratory management is associated with oxygen toxicity as lung injury. 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 ALI risk is increased among infant with excessive FiO_2 values.[2]

Wilinska et al. reports that frequent increases FiO_2 in response to dropped SpO_2 are often not meet equal attention in reduction of FiO_2 at the face of high SpO_2.[14] We observed this situation in our study also. In our analysis, FiO_2 were higher among young infants (75%) for 24-48 hours or maximum ventilatory period. There is no purpose of continuing oxygen after its requirement, must be ceased to avoid ventilator induced lung injuries. Further studies are needed to quantify oxygen exposure timing during ventilation of neonates to prevent lung injury.

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. The study population was diverse in frequency of desaturation, weight, and mode of respiratory support. A good, detailed randomized study involving the emergency situation of neonatal resuscitation is very difficult.

Conclusions:

Conventional high FiO_2 unnecessary liberal oxygen therapy in mechanically ventilated neonates improves SpO_2 but may causes iatrogenic lung injury. So, it is conceivable for the clinicians to reduce FiO_2 as soon as possible for maintain lower levels of PaO_2 with deserved SpO_2 values to ensure lung protective ventilation.

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