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# Incidence of hyperoxia and excess of oxygen use in critically ill pediatric patients

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**Author`s Contribution**

*[1,5,6] Data collection, data interpretation, drafting, and literature review*

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## ABSTRACT

**Introduction:** Oxygen therapy is a crucial aspect of quality care in the pediatric Intensive Care unit. It is not only necessary for preventing hypoxia but also important for reducing the burden of labored breathing in a child maintaining saturation at the cost of a higher basal metabolic rate. To determine the incidence of hyperoxia in patients receiving supplemental oxygen therapy in a pediatric intensive care setting.

**Methodology:** A cross-sectional prospective study was conducted at the pediatric intensive care unit of Shifa International Hospital from November 2022 to October 2023. A total of 137 patients were included in the study. Consecutive non-probability sampling was used for patients who matched the inclusion and exclusion criteria. Data regarding demographic and clinical factors was collected and evaluated using SPSS 23. The incidence of hyperoxia and its relationship to mortality, organ dysfunction, mode of ventilation, and length of stay was determined.

**Results:** The mean age of the patients participating in the study was 4.97 ± 4.35 years and 101 (73.7%) were males. Mean fractional inspired oxygen, saturation, and partial pressure of oxygen were 0.37 ±0.19, 94.58 ±3.20, and 102.77 ±21.95 mmHg respectively. The overall incidence of hyperoxia was 9.5%. There was no statistically significant difference in mode of ventilation, organ dysfunction, and length of stay when compared between those who had hyperoxia and those who did not.

**Conclusion:** The study concludes that the overall incidence of hyperoxia remains low at 9.5% as only 13 out of 137 patients experienced it.

**Keywords:** *Hyperoxia, Oxygen, Mortality, Pediatric Intensive Care, Ventilation.*

## Introduction

Oxygen therapy is a crucial aspect of quality care in the pediatric Intensive Care unit. It is not only necessary for preventing hypoxia but also important for reducing the burden of labored breathing in a child maintaining saturation at the cost of a higher basal metabolic rate. Small children tend to have fewer fat stores and energy reserves. Therefore, such children are at increased risk of type 2 respiratory failure from exhaustion. Oxygen therapy is also indicated in patients at increased risk of organ hypoperfusion. Hypoxia may be a result of poor gaseous exchange at the lungs or tissue level such as in pneumonia and sepsis, respectively. While there may be a difference in the optimum oxygen saturation targets recommended for patients in different clinical settings, there is agreement on the need for oxygen therapy to avoid hypoxia. World Health Organization generally recommends oxygen therapy for anyone with saturations below 90%.[1] Meanwhile, the American Heart Association advocates for target saturations between 94% and 99%.[2] However, studies also demonstrate that excessive oxygen saturation can lead to adverse outcomes in the pediatric population. Hyperoxia is found to be associated with higher mortality in critically ill children.[3] Supplementing spontaneous breathing with exogenous oxygen is a common medical treatment. However, it must also be considered a treatment modality in itself because no drug is without its adverse effects. It is beneficial but not completely benign. Similarly, while oxygen therapy may be necessary for sustaining life, it should not be considered completely benign. While oxygen metabolism in the human body produces vital molecules like adenosine triphosphate, it also produces reactive oxygen species. When the levels of these reactive agents exceed the antioxidant activity of blood enzymes it results in a state called oxidative stress.[4]

However, this is largely based on theoretical knowledge. Carr et al published a clinical study in 2020 that was based on critically ill patients. It revealed that the difference in blood levels of molecules produced as a result of oxidative metabolism in patients receiving conservative oxygen therapy was statistically non-significant when compared to those receiving standard therapy.[5] Previously, most research concerning hyperoxia was focused on neonates with retinopathy of prematurity and bronchopulmonary dysplasia being the most common themes.[6] Researchers are now interested to find out if higher oxygen levels in the blood of pediatric and adult patients (that is, those beyond the neonatal age) have similar risks. Morbidity and mortality have been evaluated for their association with hyperoxia in critically ill pediatric patients.[7]

However, in the absence of robust clinical trials, most guidelines for pediatric patients regarding optimum saturation targets are based on expert opinions and international consensus amongst colleagues including the European Resuscitation Council guidelines on pediatric life support.[8] The objective of our study is to determine the incidence of hyperoxia in patients receiving supplemental oxygen in pediatric intensive care via invasive or non-invasive ventilation and its relationship with mortality, length of stay, multi-organ dysfunction, and mode of ventilation.

## Methodology

A single-center cross-sectional prospective study was conducted at the pediatric intensive care unit of Shifa International Hospital, Islamabad from November 2022 to October 2023. Ethical review board approval was obtained before the study vide letter number IRB # 481-23 dated 10-Nov-2023. The sample size was calculated using the open sample size calculator. Taking the frequency of hyperoxemia at 15% with a confidence interval of 90% and absolute precision of 5%, the estimated sample size was calculated as 137 patients. Non-consecutive sampling was employed. All patients who reported to the department during the study period and met the criteria were included in the study. Written informed consent was taken from the parents or guardians of patients included in the study.

Inclusion criteria included all children between the ages of one year and 15 years who received supplemental oxygen therapy either non-invasively as High flow nasal cannula, continuous positive airway pressure, bi-level positive airway pressure, and nasal cannula or invasively through the endotracheal tube via mechanical ventilation in the first 24 hours of admission in the pediatric intensive care unit. Exclusion criteria included patients not willing to participate in the study. Also, children who died or were discharged within 24 hours of admission were not included in the study. Children with cyanotic heart diseases and methemoglobinemia, acquired or congenital were excluded. Any child who had a previously diagnosed hemoglobinopathy such as thalassemia or sickle cell disease that would affect the oxygen-binding capacity of blood was also excluded. Further to this principle, children with hemoglobin below 10mg/dL were not included to remove confounders from the study.

Demographic data was collected regarding their age, gender, any co-morbid conditions, and whether they received invasive or non-invasive supplemental oxygen therapy. Data was collected by a team of pediatricians working in the PICU and shared with the author who entered it into SPSS 23 for further analysis. Clinical data included fractional-inspired oxygen concentration received and the saturations detected on a pulse oximeter attached to a cardiopulmonary monitor at the time of blood gas analysis. The partial pressure of oxygen was also noted for each of these patients after 24 hours of receiving oxygen therapy.

Hyperoxemia is defined as saturations greater than or equal to 98% or partial pressure of oxygen greater than or equal to 100mmHg. Excess oxygen usage is defined as

Fractional oxygen greater than or equal to 0.50 in any patient experiencing hyperoxemia.

Descriptive statistics were used to describe the relevant data. Mean and standard deviation were used for the age of the patient, fractional inspired oxygen, saturations, partial pressures of oxygen, and length of stay in Paediatric intensive care. Gender, presence of co-morbid, mode of ventilation, mortality, and morbidity (in terms of MODS) were described in percentages. Pearson chi-square was used to compare mortality, MODS, and mode of ventilation between patients who experienced hyperoxia and those who did not. An Independent t-test was employed to compare the length of stay between the two groups. SPSS-23.0 was the software used to process all the data and perform the analysis. Differences between groups were considered significant if p-values were less than or equal to 0.05.

## Results

A total of 137 patients admitted to the pediatric intensive care unit of our hospital receiving supplemental oxygen therapy were included in the study. The mean age of participants in the study was 4.97 ± 4.35 years. Table 1 describes the demographics and clinically relevant data of patients participating in the study. A total of 101 (73.7%) patients were male and 36 (26.3%) were females. 78 (56.9%) patients were ventilated invasively while 59 (43.1%) were on non-invasive modes of ventilation such as high-flow nasal cannula, continuous positive airway pressure, bi-level positive airway pressure, and low-flow nasal cannula. 77 (56.2%) patients had preexisting co-morbid conditions while 60 (43.8%) did not.

The mean fractional inspired oxygen provided to patients was 0.37 ± 0.19 while the mean saturations recorded over these patients were 94.58 ± 3.2%. The mean of partial pressures of oxygen as determined by arterial blood gases was 102.77 ± 21.95 mmHg. Overall, 13 (9.5%) patients experienced hyperoxia while 124 (90.5%) maintained saturations within the recommended range. Table 2 illustrates the comparison of various factors between those experiencing hyperoxia and those who did not. Pearson chi-square determined that there was a significant difference in mortality between the two groups. Mortality was only 29 (23.4%) in the group not having hyperoxia while it was 7 (53.8%) in the group experiencing hyperoxia. The P-value was 0.018 which was considered statistically significant. The average length of stay was 5.52 ± 3.85 days in the group without hyperoxia but 5.00 ± 1.15 days in those with hyperoxia.

**Table 1: Characteristics of patients**

| Parameters | | Frequency |
|---|---|---|
| Age | | 4.97 ± 4.35 years |
| Gender | Male | 101 (73.7%) |
| | Female | 36 (26.3%) |
| Mode of ventilation | Invasive | 78 (56.9%) |
| | Non-Invasive | 59 (43.1%) |
| Co-morbidities | Yes | 77 (56.2%) |
| | No | 60 (43.8%) |
| Oxygen levels | FiO2 | 0.37 ± 0.19 |
| | SaO2 | 94.58 ± 3.20% |
| | PaO2 | 102.77 ± 21.95 mmHg |
| Hyperoxia | Yes | 13 (9.5%) |
| | No | 124 (90.5%) |

**Table 2: Relationship of various factors amongst children with hyperoxia.**

| Factors | No hyperoxia | Hyperoxia | P-value |
|---|---|---|---|
| **Mortality** | | | |
| No | 95 (76.6%) | 6 (46.2%) | 0.018* |
| Yes | 29(23.4%) | 7 (53.8%) | |
| **MODS** | | | |
| No | 72 (58.1%) | 10 (76.9%) | 0.271* |
| Yes | 51 (41.9%) | 3 (23.1%) | |
| **Mode on ventilation** | | | |
| Invasive | 68 (54.8%) | 10 (76.9%) | 0.187* |
| Non-invasive | 56 (45.2%) | 3 (23.1%) | |
| Length of stay | 5.52 ±3.85 | 5.00±1.15 | 0.126** |

*Pearson Chi-square test; **Independent T-test

The difference was not significant with a p-value of 0.126 as per the independent t-test. P-values were 0.187 and 0.271 for a mode of ventilation and multi-organ dysfunction between the 2 groups respectively hence considered non-significant.

## Discussion

Currently, Pakistan has only 1 PICU bed for every 500,000 children 14 years of age.[9] Being a developing country with limited resources, Pakistan needs to use its resources wisely. It is even more pertinent to be cautioned in cases where the resource if used excessively may be harmful to the patient. Fayazi et al conducted a retrospective study collecting data from patient records. Analyzing 64 patients revealed that in this particular pediatric intensive care unit patients were hypoxemic almost 61% of their time on supplemental oxygen.[10] Though, our study did not assess the duration of hyperoxia, the incidence was much less compared to this study. A systematic literature review of 13 studies was conducted in 2021 by Napolitano et al. It recommended that disease-specific saturation targets should be set for each child at the time of admission. This revealed a better result in terms of prognosis for the child.[11]

While our study set the hyperoxia cut-off at 98% or more, some studies advocate lower oxygen saturation targets. Cunningham et al investigated if oxygen saturation targets of 90% brought any difference in outcomes as compared to a target of 94%. It was found that a target of 90% led to an earlier discharge while bringing about no significant difference in adverse events.[12] Lillien et al conducted a systematic review of the literature of 16 studies that included more than 27 thousand patients. It concluded that while the definition of hyperoxia may vary amongst set-ups, it invariably led to increased mortality with an odds ratio of 1.5. This is similar to our study which found a statistically significant difference in mortality between the two groups.[13]

There have been no local studies in Pakistan to evaluate the effect of hyperoxia in human patients in Pakistan. However, Raza et al experimented with rats to assess the effect of hyperoxia on weight, fasting blood glucose levels, and its potential role in treating obesity. Results showed increased weight and fasting blood glucose in rats receiving hyperoxia hence proving it not a useful treatment for obesity.[14]

In 2020, Mackle and colleagues published a study in the New England Journal of Medicine. This randomized trial exhibited no significant difference in ventilator-free days between the two groups receiving liberal versus conservative oxygen therapy. This particular trial revealed that mortality in the group receiving conservative and liberal oxygen therapy was 35.7% and 34.5% respectively. With an odds ratio of 1.05, it can not entirely vouch for the safety of liberal oxygen usage or justify its usage in intensive care settings.[15] Though the figures from our study had more differences in percentages between the two groups, neither study revealed a statistically significant difference.

A clinical practice guideline published in the British Medical Journal in 2018 strongly urges maintaining oxygen saturations of no more than 96% in medical patients.[16] Certain research analyses advocate higher oxygen saturation targets in peri-operative patients such as a meta-analysis by Cohen and colleagues that included more than 14 thousand patients from 26 trials. It concluded that the relative risk for wound infection was 0.81 in the group receiving higher levels of oxygen as compared to the lower oxygen group.[17] A recent multi-center trial was conducted by Ferrando et al in Spain that demonstrated no significant difference in surgical site infection between patients receiving fractional-inspired oxygen of 0.30 and those receiving 0.8018.

Most previous studies evaluating the role of hyperoxia on patient outcomes have focused on mortality rather than organ dysfunction. While mortality in pediatric intensive care usually lies around 2-3%, it rises drastically for any child requiring respiratory support.[19] Organ dysfunction is of prime importance in childhood. Any dysfunction, mild or severe for any period may lead to impaired organ development during periods of active growth. The OXY-PICU trial included a lung function score to address this vital concern.[20] Similarly our study included multi-organ dysfunction syndrome as one of the outcomes compared. While mortality was found to be significantly different between the two groups, the difference in organ dysfunction was statistically significant. However, it is suggested that in the future scoring should be employed to assess organ function separately.

**Limitations of the Study**

It is also imperative to note that hyperoxia-related adverse effects are also affected by the timing, duration, and extent of hyperoxia.[21-23] However, our study limitation included taking readings at a certain point in time for each patient rather than repeatedly throughout admission. Hence, we cannot comment on the duration of hyperoxia exposure in our patients.

## Conclusion

This study expands the existing clinical and epidemiological data by reviewing the current practice of oxygen therapy in a pediatric intensive care set-up in Pakistan and implementing the current standard of care to optimize the risks and benefits of this therapy in the future. The findings of this study contribute to the body of knowledge on the use of oxygen therapy in critically ill children and inform clinical practice in resource-limited settings.

## References

1. World Health Organization. Updated guideline: pediatric emergency triage, assessment and treatment: care of critically ill children. World Health Organization; 2016.
2. Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner Jr BL, et al. Part 4: Pediatric Basic and advanced life support: 2020 American Heart Association guidelines for Cardiopulmonary Resuscitation and emergency cardiovascular care. Circulation. 2020; 142(16_Suppl_2):S469-523.
DOI: https://doi.org/10.1161/CIR.0000000000000901.
3. Ralston SL, Lonhart JA, Schroeder AR. Too much of a good thing: Hyperoxia and pediatric respiratory illnesses. Pediatrics. 2020; 146(2) ):e20193343
DOI: https://doi.org/10.1542/peds.2019-3343
4. Young PJ, Frei D. Oxygen therapy for critically Ill and post-operative patients. J Anaesth. 2021; 35(6):928-38.
DOI: https://doi.org/10.1007/s00540-021-02996-8
5. Carr AC, Spencer E, Mackle D, Hunt A, Judd H, Mehrtens J, et al. The effect of conservative oxygen therapy on systemic biomarkers of oxidative stress in critically ill patients. Free Radic Biol Med. 2020; 160:13-8.
DOI: https://doi.org/10.1016/j.freeradbiomed.2020.06.018
6. Thébaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH, et al. Bronchopulmonary dysplasia. Nat Rev Dis Primers. 2019; 5(1).
DOI: https://doi.org/10.1038/s41572-019-0127-7
7. Peters MJ. Linking hyperoxia and harm: consequence or merely subsequence?. Pediat Crit Care Med. 2021; 22(5):501-3.
DOI: https://doi.org/10.1097/PCC.0000000000002709
8. Van de Voorde P, Turner NM, Djakow J, de Lucas N, Martinez-Mejias A, Biarent D, et al. European resuscitation council guidelines 2021: paediatric life support. Resuscitation. 2021; 161:327-87.
DOI: https://doi.org/10.1016/j.resuscitation.2021.02.015
9. Fayazi AR, Sesia M, Anand KJS. Hyperoxemia among pediatric intensive care unit patients receiving oxygen therapy. J Pediatr Intensive Care. 2021;
DOI: https://doi.org/10.1055/s-0041-1740586
10. Napolitano N, Berlinski A, Walsh BK, Ginier E, Strickland SL. AARC clinical practice guideline: Management of pediatric patients with oxygen in the acute care setting. Respir Care. 2021; 66(7):1214-23.
DOI: https://doi.org/10.4187/respcare.09006
11. Cunningham S, Rodriguez A, Adams T, Boyd KA, Butcher I, Enderby B, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomized, equivalence trial. Lancet. 2015; 386(9998):1041-8.
DOI: https://doi.org/10.1016/S0140-6736(15)00163-4
12. Lilien TA, Groeneveld NS, van Etten-Jamaludin F, Peters MJ, Buysse CMP, Ralston SL, et al. Association of arterial hyperoxia with outcomes in critically ill children: A systematic review and meta-analysis: A systematic review and meta-analysis. JAMA Netw Open. 2022; 5(1):e2142105.
DOI: https://doi.org/10.1001/jamanetworkopen.2021.42105
13. Raza M, Ali S. Fasting Blood Glucose and Serum Peptide YY levels in Sprague Dawley Rats and its Potential role in Treating Obesity. J Islamic Int Med Coll. J. 2017; 12(2):78-82
14. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020; 382(11):989-98.
DOI: https://doi.org/10.1056/NEJMoa1903297
15. Siemieniuk RAC, Chu DK, Kim LH-Y, Güell-Rous M-R, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ [Internet]. 2018; 4169.
DOI: https://doi.org/10.1136/bmj.k4169
16. Cohen B, Schacham YN, Ruetzler K, Ahuja S, Yang D, Mascha EJ, et al. Effect of intraoperative hyperoxia on the incidence of surgical site infections: a meta-analysis. Br J Anaesth. 2018; 120(6):1176-86.
DOI: https://doi.org/10.1016/j.bja.2018.02.027
17. Ferrando C, Aldecoa C, Unzueta C, Belda FJ, Librero J, Tusman G, et al. Effects of oxygen on post-surgical infections during an individualized perioperative open-lung ventilatory strategy: a randomized controlled trial. Br J Anaesth. 2020; 124(1):110-20.
DOI: https://doi.org/10.1016/j.bja.2019.10.009
18. Burns JP, Sellers DE, Meyer EC, Lewis-Newby M, Truog RD. Epidemiology of death in the PICU at five U.S. teaching hospitals. Crit Care Med. 2014; 42(9):2101-8.
DOI: https://doi.org/10.1097/ccm.0000000000000498
19. Peters MJ, Jones GA, Wiley D, Wulff J, Ramnarayan P, Ray S, Inwald D, et al. Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. Intensive Care Med. 2018; 44:1240-8.
DOI: https://doi.org/10.1007/s00134-018-5232-7
20. Ketharanathan N, De Jonge RCJ, Klouwen I, Wildschut ED, Reiss IKM, Tibboel D, et al. Hyperoxia in pediatric severe traumatic brain injury (TBI): a comparison of patient classification by cutoff versus cumulative (area-under-the-curve) analysis. Brain Inj. 2020; 34(7):958–64.
DOI: https://doi.org/10.1080/02699052.2020.1765021
21. Ramgopal S, Dezfulian C, Hickey RW, Au AK, Venkataraman S, Clark RSB, et al. Association of severe hypoxemia events and mortality among patients admitted to a pediatric intensive care unit. JAMA Netw Open. 2019; 2(8):e199812.
DOI: https://doi.org/10.1001/jamanetworkopen.2019.9812.