**Arterial hyperoxemia and acute kidney injury in trauma patients: a retrospective observational study**

**Background:**

Oxygen (O2) is essential for humans and the consequences associated with hypoxemia can be devastating. While O2 has been widely prescribed for therapy in medicine (1), there is an emerging concern that hyperoxemia (increased PaO2) could also embrace potential detrimental systemic effects (2).

Hyperoxemia can induce cellular damage through excess reactive oxygen species and can have negative hemodynamic effects by inducing systemic vasoconstriction (3) (4). Recently, the potentially harmful impact of oxygen has been studied in clinical trials across multiple fields, including cardiopulmonary resuscitation (5) (6), stroke (8), myocardial infarction (9), traumatic brain injury (10) and medical-surgical intensive care (11).

Considering the suggested injurious mechanisms, kidney function could be one of the targets for hyperoxemia toxicity. Animal studies have shown the detrimental effect of hyperoxemia on renal tissue through protein expression associated with inflammation and imbalance of renal oxygen delivery and demand (12) (13). In humans, a strong association between acute kidney injury and mortality (14) was been shown and the potential impact of hyperoxemia on kidney function could be a major concern.

O2 might be the most commonly administered drug in trauma settings. Since significant hypoxemia after trauma can quickly lead to a fatal event, liberal oxygen therapy is provided either in response to or for prevention of hypoxic organ damage. However, the impact of keeping supranormal arterial blood oxygen tensions during the ICU stay on the development of acute kidney injury (AKI) in critically injured patients remains unclear.

**Research Hypotheses:**

We hypothesize that hyperoxemia, as compared with normal oxygen levels is associated with renal dysfunction in trauma patients between 48 hours and up to 7 days of the ICU stay.

**Research Question / Objective:**

The aim of this study is to survey the prevalence and the degree of hyperoxemia among trauma patients in an intensive care unit and to investigate the association between PaO2 and the development of AKI. Our research question is how the time-weighted average PaO2 during the first 24 hours of the ICU stay is associated with the development of AKI.Development of AKI is defined as the primary outcome using Kidney Disease Improving Global Outcomes (KDIGO) consensus criteria (7).

**Data Sources:**

MIMIC-III (Medical Information Mart for Intensive Care III) database will be used for this study. It comprises deidentified health-related data associated with over forty thousand patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012.

The eICU Collaborative Research Database may be utilized if analysis on MIMIC-III deem it is necessary to incorporate a larger database.

**Study Population:**

Inclusion criteria:

* 18 years old and older
* Trauma patients who are defined by using International Classification of Disease, 9th Revision, Clinical Modification codes: 800 – 956 for ICD9
* Patients who, directly or through the operation room, admitted to the ICU
* Patients who stayed in the ICU for at least 48 hours

Exclusion criteria:

* Preexisting chronic kidney dysfunction and hemodialysis
* Patients without ABG measurements, creatinine and/or urine output
* Patients after cardiopulmonary resuscitation
* Patients with Comfort Measures Only (CMO) order

**Study Outcomes:**

The primary outcome will be defined as AKI (fulfilling the KDIGO criteria) during the first 24 hours or 7 days of the ICU stay. The secondary outcomes are all-cause mortality, length of stay in the ICU and hospital length of stay, and duration of mechanical ventilation and start of renal replacement therapy.

**Covariate(s) of Interest (Exposure):**

Patients will be divided based on quartiles/quintiles of mean PaO2 levels during the first 24 hours of the ICU stay. This ensures an equal number of participants in each group and is an objective way of classifying exposure levels.

**Confounders:**

We will adjust for the following confounders: age, gender, disease severity (APACHE IV), amount of transfused blood products (blood loss), preexisting kidney disease, preexisting heart disease, diabetes mellitus, chronic lung disease, nephrotoxic medication (NSARS, nephrotoxic antibiotics).

**Statistical analysis**

We will fit the Cox proportional hazard model to evaluate the association of categorized PaO2 levels with the incidence of AKI and secondary outcomes. Time to event will be calculated from the day of hospital (all-cause mortality) or ICU (ICU LOS) admission until the experience of the event or until the KDIKO criteria are met (AKI). We will fit a multivariable model adjusting for the above-mentioned confounders. A proportional hazard analysis using Schoenfeld residuals and Schoenfeld’s global test will be utilized to decide whether to reject the proportional hazard assumption. We will also test the linearity assumption and ensure the model fit.

As sensitivity analyses, we will use different exposure levels of mean PaO2 for the first 6, 12, 24 and 48 hours and observe the effect on the onset of AKI within 48 h and 7 days after ICU admission. We will also investigate the effect of changing exposure (mean PaO2) on the onset of pre-defined secondary outcomes.

All analyses will be performed using the open-access software *R* (version 3.4, <http://www.R-project.org/>) and relevant packages. All tests will be two-sided and will have an alpha-level of 0.05 to determine statistical significance.

**Acknowledgements:**

This manuscript has been produced as part of course HST.953 at the Massachusetts Institute of Technology, Cambridge, MA, USA.

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