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Neurological outcomes and mortality of hyperoxaemia in patients with acute brain injury: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Oxygen is frequently prescribed in neurocritical care units. Avoiding hypoxaemia is a key objective in patients with acute brain injury (ABI). However, several studies suggest that hyperoxaemia may also be related to higher mortality and poor neurological outcomes in these patients. The evidence in this direction is still controversial due to the limited number of prospective studies, the lack of a common definition for hyperoxaemia, the heterogeneity in experimental designs and the different causes of ABI. To explore the correlation between hyperoxaemia and poor neurological outcomes and mortality in hospitalised adult patients with ABI, we will conduct a systematic review and meta-analysis of observational studies and RCTs.

Methods and analysis The systematic review methods have been defined according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and follow the PRISMA-Protocols structure. Studies published until June 2024 will be identified in the electronic databases MEDLINE, Embase, Scopus, Web of Science, The Cochrane Library, Cumulative Index to Nursing and Allied Health Literature and ClinicalTrials.gov. Retrieved records will be independently screened by four authors working in pairs, and the selected variables will be extracted from studies reporting data on the effect of 'hyperoxaemia' versus 'no hyperoxaemia on neurological outcomes and mortality in hospitalised patients with ABI. We will use covariate-adjusted ORs as outcome measures when reported since they account for potential cofounders and provide a more accurate estimate of the association between hyperoxaemia and outcomes; when not available, we will use univariate ORs. If the study presents the results as relative risks, it will be considered equivalent to the OR as long as the prevalence of the condition is close to 10%. Pooled estimates of both outcomes will be calculated applying random-effects meta-analysis. Interstudy heterogeneity will be assessed using the I^2 statistic; risk of bias will be assessed through Risk Of Bias In Non-Randomised Studies of Interventions, Newcastle-Ottawa or RoB2 tools. Depending on data availability, we plan to conduct subgroup analyses by ABI type (traumatic brain injury, postcardiac arrest, subarachnoid haemorrhage, intracerebral haemorrhage and ischaemic stroke), arterial partial pressure of oxygen values, study quality, study time, neurological scores and other selected clinical variables of interest.

Ethics and dissemination Specific ethics approval consent is not required as this is a review of previously published anonymised data. Results of the study will be shared with the scientific community via publication in a peer-reviewed journal and presentation at relevant conferences and workshops. It will also be shared key stakeholders, such as national or international health authorities, healthcare professionals and the general population, via scientific outreach journals and research institutes' newsletters.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This meta-analysis will yield updated estimates of the effect of 'hyperoxaemia' versus 'no hyperoxaemia' on poor neurological outcomes and mortality in patients with acute brain injury and each of its main causes; up to date, no reviews covering this subset of intensive care unit patients have been published in the field.

⇒ The variability in the definition of hyperoxaemia has remained a consistent limitation in previous studies; here, we will include studies which use partial pressure of oxygen (PaO2) as measure of oxygenation, we will maintain the PaO_2 threshold value chosen by each individual and we will perform subgroup analyses according to oxygenation thresholds.

⇒ A meta-regression will be applied to explore the impact of different oxygenation levels on the outcomes, providing a more detailed understanding of the effects of varying oxygen levels.

⇒ Risk of bias analysis will be performed after record screening; unlike previous reports, we will perform subgroup analyses focusing only on studies with low/moderate risk of bias.

⇒ Several sources of heterogeneity may not be controlled, such as timing and duration of hyperoxaemia, timing of survival analysis and neurological scores used to define poor neurological outcomes.

BACKGROUND

Acute brain injury (ABI) is an umbrella term for several conditions leading to sudden, acquired neuronal damage: traumatic brain injury (TBI), postcardiac arrest (PCA) brain injury, subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH) and ischaemic stroke (IS).[1 2] ABI gathers a high global incidence, which is estimated at 939/100 000 person-years for TBI,[3] 14.46 for SAH, 41.81 for ICH and 98.62 for IS (age-adjusted rates).[4] For some of these conditions, the incidence is expected to increase parallel to the age of population over the next decade.[5] In addition to the high mortality rates it entails,[4] ABI is associated with a significant neurological impairment and carries a non-negligible socioeconomic cost,[6 7] which is particularly burdensome in low-income and middle-income countries.[8 9]

Optimal brain oxygenation stands as the paramount target in neurocritical patients.[1 10] Therefore, supplemental oxygen is often required to prevent further damage, together with other determinants of cerebral oxygenation such as adequate haemoglobin levels and cerebral blood flow regulation.[1] Hypoxaemia, which is defined as an arterial partial pressure of oxygen (PaO_2) lower than 80 mm Hg, has been related to in-hospital mortality in subsets of ABI.[11–14] Experimentally, hypoxaemia causes sodium-potassium ATPase dysfunction and mitochondrial damage, leading to cell death.[15 16] Preclinical findings suggesting that normobaric oxygen could act as a neuroprotectant and improve outcomes in IS[17–19] have, nonetheless, proven inconsistent in clinical trials involving non-hypoxaemic patients.[20 21] The same may be true for other ABI-related conditions.

In fact, more recent studies suggest that liberal oxygenation strategies may also have detrimental effects in mortality and neurological outcomes compared with conservative strategies in general intensive care unit (ICU) patients,[22–24] and particularly in ABI patients.[25–27] A marked release of reactive oxygen species and proinflammatory cytokines, which damage DNA and predispose to cell death, as well as coronary ischaemic events due to sustained arterial vasoconstriction, or alveolar membrane damage, are some of the consequences of hyperoxaemia according to preclinical models,[28–30] accounting for both higher mortality and worse neurological outcomes.[31] Treatment with antioxidant compounds, such as L-carnitine, may provide benefits in these patients.[32] There is no agreement on the threshold value for defining hyperoxaemia, but most authors concur on a PaO_2 of 200–300 mm Hg for severe hyperoxaemia.[10] According to recent literature, a PaO_2 as low as 195 mm Hg[33] or even 156 mm Hg[2] can be related to lower survival in patients with ABI. A U-shaped curve may accurately represent the correlation between arterial oxygenation and survival or neurological outcomes in patients with ABI, but further studies are required in this specific population.[2 33]

Although previous reviews on the topic have been published, there is a strong rationale for updating these works. First, most reviews do not focus specifically on patients with ABI but include ICU-admitted patients with different diagnosis, such as sepsis or cardiac surgery.[34–36] Second, some of them share different outcome measures, such as inspired fraction of oxygen (FiO_2), peripheral oxygen saturation ($SatO_2$) and PaO_2, or include both hypoxaemic and normoxaemic patients in the control group, which may introduce a source of heterogeneity in results.[22 24] Another source of heterogeneity is the different thresholds for 'hyperoxaemia'and 'no hyperoxaemia' in each study, which could be tackled through a common definition.[34–36] Finally, new results have recently emerged in the field that should be included in updated reviews. In this context, the aim of the proposed systematic review is to analyse whether arterial hyperoxaemia influences mortality and neurological outcomes in ABI. The aim of the proposed meta-analysis is to derive estimates on the effect of hyperoxaemia neurological outcomes and mortality in adult hospitalised patients with ABI. These data could provide strong evidence to guide ventilatory strategies and ultimately reduce iatrogenic risks in neurocritical ICUs.

METHODS/DESIGN

The review design has been defined following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[37] This protocol was developed according to the PRISMA-Protocols checklist[38] (online supplemental appendix 1). The study has been registered on PROSPERO (CRD42023433502).

Criteria for considering studies

Study population and study design

Only studies reporting original data will be included in the review. We will include randomised clinical trials and observational studies. Within the latter, both prospective and retrospective cohort and case control studies will be considered. Published conference abstracts will be included in the systematic review when data for quality assessment of the database is available but excluded from meta-analysis due to lack of an underlying peer-review process. Letters to the editor, unpublished freely available studies (eg, on bioRxiv), case series and case reports will be excluded in order to strengthen methodological rigour. There will be no restriction on publication period or language if there is an abstract in English. Duplicate reports or studies based on the same databases will be excluded.

We will include studies based on a population with the following characteristics: (1) adult patients of any gender, over 18 years of age, (2) admitted to the hospital and (3) with a diagnosis of ABI-related condition: TBI, PCA (excluding cardiac surgery under cardiopulmonary bypass), SAH, ICH, IS. Exclusion criteria will be (1) children (under 18 years of age) and (2) previous neurological condition (dementia, cerebral palsy and others).

The studied intervention is arterial hyperoxaemia, which is defined in this review as the presence of elevated

PaO_2 under normobaric conditions. The commonly accepted threshold for hyperoxaemia is a PaO_2 over 120 mm Hg. Within this range, values between 120 and 200 mm Hg will be considered as moderate hyperoxaemia while values exceeding 200 mm Hg will be classified as severe hyperoxaemia, according to literature.[39] It should be noted that for each included study, the specific cut-off value for hyperoxaemia as defined by the authors will be adopted in our analysis, similar to previous reviews.[34 35] If studies present the result as ORs of quartiles of PaO_2 distribution, the effect estimates corresponding to the highest quartile (Q4 or Q5) will be selected for pooling. The variability arising from different approaches to presenting exposure, such as various PaO2 cutoffs to define hyperoxaemia, will be accounted for through subgroup analysis or meta-regression. We will exclude studies where intervention is either (1) non-arterial hyperoxaemia, (2) hyperoxaemia not defined using PaO2 ($SatO_2$, FiO_2…) or (3) hyperbaric oxygenation.

The most expected presentation will be a three-level category variable: hyperoxaemia, normoxaemia and hypoxaemia. The comparator or control group will be 'no hyperoxaemia', which may include normoxaemia, hypoxaemia or both, depending on the definition of each individual study. Whenever possible, we will use exposure to normoxaemia as comparator, which will be defined as a lower limit of PaO_2 over 60 mm Hg. However, studies using a lower PaO_2 threshold for normoxaemia, or the pooling of hypoxaemia and normoxaemia, or the PaO_2 range included in Q1 (for quartiles or quintiles presentation), as comparators, will also be considered. Where no lower limit of PaO_2 is defined, authors will be contacted to clarify.

DEFINITIONS AND OUTCOME MEASURES

The primary outcome is the occurrence of poor neurological outcome in patients with ABI exposed to hyperoxaemia. Neurological outcomes are often reported using Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), GOS Extended (GOS-E), Cerebral Performance Category (CPC), modified Rankin Score (mRS) or Barthel scores. The definition of poor neurological outcomes varies among the different studies. Some commonplace definitions in literature are GCS<9, GOS<4, GOSE<4, CPC>2 and mRS>3. We will adopt the definition of poor neurological outcomes from each study at the longest period of follow-up, similar to previous reviews.[35] Secondary outcome is all-cause mortality. The timing of mortality measures will be at hospital discharge (in-hospital mortality) when reported; otherwise, we will choose the next available period of follow-up.

We will estimate OR for poor neurological outcomes and mortality in the different ABI-related conditions, provided a covariate-adjusted OR, or an unadjusted OR, or a 2×2 cross-tabulation table is reported. Covariate-adjusted ORs, derived from multivariable analysis, provide a more accurate estimate of the association between hyperoxaemia and outcomes. They account for potential confounders, offering a clearer understanding of the true effect of hyperoxaemia. This is particularly important in clinical scenarios such as the case of ABI—a complex condition influenced by numerous factors like age, severity of injury, comorbidities and treatment modalities. Univariate ORs in this setting will fail to account for these confounding variables, potentially leading to biased estimates of the effect of hyperoxaemia where multiple factors can influence patient outcomes. For poor neurological outcomes as well as for the mortality endpoint, the covariate-adjusted ORs with 95% CI will be extracted from each study. If the study presents the results as relative risks (or risk ratio, RR), it will be considered equivalent to the OR as long as the prevalence of the condition is close to 10%. Studies where the effect size reported is an unadjusted OR, or equivalently, those studies where the OR was estimated based on a 2×2 cross-tabulation table will be analysed separately from the covariate-adjusted studies. Studies with the effect size reported as HRs will not be included.

Search methods for identification of studies

Relevant studies will be identified by searching the electronic databases: MEDLINE (Ovid; 1946 to the present), Embase (Ovid; 1947 to the present), Scopus (2004 to the present), Web of Science (1900 to the present), The Cochrane Library (Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews), Cumulative Index to Nursing and Allied Health Literature (1937 to the present) and ClinicalTrials.gov (2000 to the present). Additional studies will be found in previous systematic reviews, reference lists of included articles and experts' opinions to include all relevant works and minimise publication bias. Authors will be contacted over institutional email during the first month of the study for further information or clarification when relevant data are missing; a second reach will be attempted two weeks from the first if there is no response. The search will not be restricted to specific publication types or languages provided an abstract in English is available. We will use search keywords related to "hyperoxemia", "mortality", "neurological outcome/disability", "human" and "acute brain injury" from different causes ("traumatic brain injury", "cardiorespiratory arrest", "subarachnoid hemorrhage", "intracerebral hemorrhage" and "ischemic stroke"). The search strategy (online supplemental appendix 2) will be reviewed by a librarian at University of Valencia. The last search will be on 1 June 2024.

Data collection and analysis

Study selection

Included studies will be grouped and duplicates removed through a reference management software package (EndNote V.21, Clarative Analytics). A two-step independent process will be performed by two pairs of reviewers, who will assess identified studies for eligibility according to previously defined inclusion and exclusion criteria. A first

screen will be based on the title and abstract (AR-Z and MP-G), and a second screen will be based on full text (AR-P and FP). Duplicate publications of the same study will be checked by comparing title, author names, study population, exposure and outcomes. The publication with the lowest risk of bias will be included or, where publications have an equal risk of bias, we will include the study with a larger sample size. In case it is unclear whether the publications belong to the same study, corresponding authors will be contacted. Screened references and the criteria accounting for exclusion will be reported in a data sheet.

At both steps, intercoder agreement will be assessed through Cohen's κ, a minimum κ value of 0.75 representing high agreement.[40] Discrepancies between authors will be resolved by a third author (BM), independently of κ value. The studies' selection process will be represented in a PRISMA flow chart.

Data extraction and management

Data will be extracted in duplicate by two independent reviewers using a predefined data collection form (DCF). The DCF will be tested and validated through a pilot study on thirty random articles and refined accordingly. Variables in the DCF are the following:

1. Study details: Title, first author, year of publication, corresponding author, study design, country and continent, inclusion, and exclusion criteria.
2. Population: Principal diagnosis, additional cohort information, mean age and gender, the number of patients.
3. Exposure: Type of ventilatory support, type of PaO_2 recorded (first, highest, lowest), definition of hyperoxaemia (PaO_2 threshold or range) and control groups, duration of hyperoxaemia.
4. Outcome: Main outcome, time of mortality measurement, neurological outcome score recorded, definition of poor neurological outcome, time of neurological outcome measurement.
5. Results: The number of patients with hyperoxaemia, the number of patients with normoxaemia, the number of deceased patients in each group, the number of patients with poor neurological outcome in each group, adjusted ORs or RRs with 95% CIs for mortality in hyperoxaemia versus no hyperoxaemia group and its p value, adjusted ORs or RRs with 95% CIs for poor neurological outcomes in hyperoxaemia versus no hyperoxaemia group and its p value, adjusting factors, mean and median PaO_2 with SE in each group.

Analysis and data synthesis

To report qualitative data, the characteristics and findings from included studies will be summarised in a table. The table will include the following variables: first author, year of publication, study design, population, principal diagnosis, ventilation type, PaO_2 type, hyperoxaemia and control definition, main outcome, time of mortality measures, neurological outcome score and time, poor neurological outcome definition.

For quantitative synthesis, we will estimate OR for poor neurological outcomes and mortality endpoints based on either a covariate-adjusted OR, on an unadjusted OR, or on a 2×2 cross-tabulation table extracted from each study. If the study presents the results as RRs, it will be considered equivalent to the OR as long as the prevalence of the condition is close to 10%. Studies where the effect size reported is an unadjusted OR, or equivalently, those studies where the OR was estimated based on a 2×2 cross-tabulation table will be analysed separately from the covariate-adjusted studies. Studies with the effect size reported as HRs will not be included. Similar approach will be followed for the mortality endpoint, assuming that due to the short interval in the evaluation of the endpoint, the study presents the effect size as OR (or RRs). Studies that present the result as HRs will not be included in the meta-analysis. The reasons fo this exclusion are (1) these studies usually have longer follow-up (1-year minimum), (2) the time of outcome measure will be adopted from every individual study and not recalculated at an arbitrary time point, in order to minimise bias and (3) it is difficult to convert the HR to RR in the absence of data which is not easily available (the number of censored events at every time point), which precludes pooling the effect of the other studies (such as OR). Covariate-adjusted estimates will be our first choice for pooling.

In assessing the association between hyperoxaemia (vs the comparator group) with regard to poor neurological outcome, the OR/RR will be the most common effect size. However, if poor neurological outcome is represented as a continuous variable, we will employ the standardised difference based on Hedges's g method as the effect size for comparison. Covariate-adjusted estimates will be our first choice for pooling. Statistical heterogeneity will be estimated using the I^2 and the p value of Cochrane Q χ^2 test, with a cut-off value of 0.05 for statistically significant heterogeneity. I^2 value of 25%–50% represents low heterogeneity, 50%–75% moderate heterogeneity and >75% high heterogeneity. A random-effects restricted maximum likelihood (REML) method will be used for pooling the results, independently of p value since our protocol considers the inclusion of a highly variable population with potentially different outcome measures and the random-effects method is the most appropriate to represent this variability.

We plan to perform subgroup analysis according to the following variables:

1. Mechanism of ABI: If possible, subgroup analyses will be performed according to the mechanism of ABI (TBI, SAH, ICH, IS or postcardiorespiratory arrest).
2. Neurological criterion for evaluation: If possible, subgroup analyses of the meta-analysis will be considered according to the different scores used to evaluate neurological outcomes.
3. Using unadjusted OR for analysis.
4. Using a fixed effect model for analysis.
5. Risk of bias: Restricting the analysis to good quality (ie, low or moderate risk of bias) publications.

6. Oxygenation thresholds: Studies with severe hyperoxaemia (PaO2>200 mm Hg or 300 mm Hg) will be further analysed. Studies with normoxaemia (PaO2 60–300 mm Hg or any upper limit for normoxaemia) as the only comparator will be further analysed.

Further subgroup analysis based on other modifiable factors will be performed if feasible.

Sensitivity analysis will be carried out considering only studies of the highest methodological quality and low/moderate risk of bias.

Meta-regression may be employed as a statistical method to examine potential factors contributing to heterogeneity among the studies included in the meta-analysis. This approach enables the investigation of various study-level characteristics or covariates that could potentially account for the observed variability in effect sizes across the studies. In our meta-analysis, meta-regression will play a crucial role in quantifying the extent of heterogeneity when pooling studies that define hyperoxaemia using different PaO2 cutoffs, as well as for studies that have solely reported the mean, median, or maximum value of PaO2.

Publication bias will be illustrated with a funnel plot of RR and the inverse of the SE and will be analysed using Egger's test. If the funnel plot is asymmetrically shaped by visual evaluation or Egger's test returns a $p<0.05$, suggesting potential publication bias, we will apply Duval and Tweedie's trim-and-fill method. For publications with missing or unclear important data, we will attempt to contact the corresponding authors to obtain the missing data.

All analyses will be performed with Stata statistical software V.18 (StataCorp).

Quality assessment

Each study will be assessed by two independent reviewers using the Risk Of Bias In Non-Randomised Studies of Interventions (ROBINS-I) or Newcastle-Ottawa Scale (NOS) for observational studies of interventions or exposures, respectively, or the Cochrane risk-of-bias tool for randomised trials (RoB 2) for randomised clinical trials (RCTs), according to current Cochrane recommendations.[41 42] A third reviewer will be contacted if consensus cannot be made. Studies will be classified as 'good' quality when (1) NOS higher than 6/9 and all domains higher than 0 or (2) RoB2 or ROBINS-I with overall score 'moderate' or 'low' risk of bias.

Regarding metabiases, a publication bias towards studies with statistically significant results may exist, which could either over or underestimate the effects of hyperoxaemia. This publication bias can be detected with the funnel plot, which will be included. A selective reporting bias could also exist, overestimating or underestimating the effects of hyperoxaemia; this will be addressed by a risk of bias assessment of the included studies, that ensures they follow their previously published protocol.

The quality of evidence for the selected outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation methodology.[43] The domains in which quality of evidence will be assessed are risk of bias, consistency, directness, precision and publication bias. Quality will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect).

Patient and public involvement

As this will be a review of published papers, primary data from patients will not be involved in the study. Data will be collected from previously published studies as described before. Authors will be contacted if further aggregated data is required.

Ethics and dissemination

Specific ethics approval consent is not required as this is a review of previously published anonymised data. Results of the study will be shared with the scientific community via publication in a peer-reviewed journal and presentation at relevant conferences and workshops. It will also be shared key stakeholders, such as national or international health authorities, healthcare professionals and the general population, via scientific outreach journals and research institutes' newsletters.

DISCUSSION

Considering the high incidence and socioeconomic burden of ABI, there is a strong rationale for updating current available evidence on the effect of hyperoxaemia on mortality and neurological outcome. As previously discussed, the last meta-analysis focused on the effect of hyperoxia on mortality and neurological outcomes in ICU include data up to 2013 and 2020, respectively, and included all ICU patients, with no restriction on admission diagnosis.[35 36] Other recent meta-analyses on the topic share a broader definition of hyperoxaemia and include $SatO_2$ or inspired oxygen fraction, which may be less accurate and induce bias.[44 45]

Our review is based on a similar methodology to Hirunpattarasilp *et al*,[35] aiming to generate comparable estimates as far as neurological outcomes are concerned. However, we intend our approach to include some modifications, such as more specific study population, the inclusion of more recent data and the mortality endpoint. Notably, unlike Hirunpattarasilp *et al*, we will perform subanalysis based on PaO2 thresholds, study quality and neurological outcome scores, in order to enhance comparability of results.

To the best of our knowledge, this is the first review having both mortality and neurological outcomes as endpoints, as well as the first review of hyperoxaemia

in patients strictly with ABI. We firmly believe that our data could shed light on the development of protocols aimed at preventing iatrogenesis in patients with ABI. Furthermore, it could help identify the PaO2 thresholds above which these iatrogenic risks escalate, as well as those subsets of patients for whom hyperoxaemia is detrimental. In conclusion, our results could help optimise resource allocation and direct future research to address knowledge gaps.

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