Resuscitation 91 (2015) 32–41

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review article

Effects of $PaCO_2$ derangements on clinical outcomes after cerebral injury: A systematic review☆

Brian W. Roberts[a,*], Paul Karagiannis[a], Michael Coletta[a], J. Hope Kilgannon[a], Michael E. Chansky[a], Stephen Trzeciak[a,b]

[a] Department of Emergency Medicine, Cooper University Hospital and Cooper Medical School of Rowan University, Camden, NJ, USA
[b] Department of Medicine, Division of Critical Care Medicine (ST), Cooper University Hospital and Cooper Medical School of Rowan University, Camden, NJ, USA

ARTICLE INFO

Article history:
Received 14 December 2014
Received in revised form 4 February 2015
Accepted 9 March 2015

Keywords:
Hypocapnia
Hypercapnia
Partial pressure of arterial carbon dioxide ($PaCO_2$)
Cerebral injury
Head injury
Brain injury

ABSTRACT

Objective: Partial pressure of arterial carbon dioxide ($PaCO_2$) is a major regulator of cerebral blood flow (CBF). Derangements in $PaCO_2$ have been thought to worsen clinical outcomes after many forms of cerebral injury by altering CBF. Our aim was to systematically analyze the biomedical literature to determine the effects of $PaCO_2$ derangements on clinical outcomes after cerebral injury.
Methods: We performed a search of Cochrane Library, PUBMED, CINHAL, conference proceedings, and other sources using a comprehensive strategy. Study inclusion criteria were (1) human subjects; (2) cerebral injury; (3) mechanical ventilation post-injury; (4) measurement of $PaCO_2$; and (5) comparison of a clinical outcome measure (e.g. mortality) between different $PaCO_2$ exposures. We performed a qualitative analysis to collate and summarize effects of $PaCO_2$ derangements according to the recommended methodology from the Cochrane Handbook.
Results: Seventeen studies involving different etiologies of cerebral injury (six traumatic brain injury, six post-cardiac arrest syndrome, two cerebral vascular accident, three neonatal ischemic encephalopathy) met all inclusion and no exclusion criteria. Three randomized control trials were identified and only one was considered a high quality study as per the Cochrane criteria for assessing risk of bias. In 13/17 (76%) studies examining hypocapnia, and 7/10 (70%) studies examining hypercapnia, the exposed group (hypercapnia or hypocapnia) was associated with poor clinical outcome.
Conclusion: The majority of studies in this report found exposure to hypocapnia and hypercapnia after cerebral injury to be associated with poor clinical outcome. However, the optimal $PaCO_2$ range associated with good clinical outcome remains unclear.

1. Introduction

Cerebral injury is a complex pathophysiologic process, which often results in death or long-term disability, making cerebral injury a major public health problem. Examples of cerebral injury include traumatic brain injury (TBI), cerebral vascular accident (CVA), and cardiac arrest. TBI is a leading cause of morbidity and mortality worldwide.[1] Approximately 1.5 million Americans experience TBI each year of which ~50,000 die[2] and among survivors many suffer long-term disability.[3] Among patients suffering from CVA requiring mechanical ventilation, mortality has been demonstrated to be as high as 72–90%.[4–6] Cerebral injury is the most common (~70%) cause of death among patients resuscitated from out-of-hospital cardiac arrest.[7] A large U.S. multi-center cohort study of patients who survived to intensive care unit (ICU) admission following successful resuscitation from cardiac arrest found that 50% of patients did not survive to hospital discharge. Of those who did survive, the majority of patients were functionally dependent, and more than half of these patients were discharged to a long-term care facility.[8]

Clinical management of many forms of cerebral injury aim to decrease hypoperfusion (either global or regional), control intracranial pressure (ICP), and improve cerebral blood flow (CBF). Partial pressure of arterial carbon dioxide ($PaCO_2$) is a

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2015.01.015.

* Corresponding author at: Department of Emergency Medicine, Cooper University Hospital, One Cooper Plaza, K152, Camden, NJ 08103, USA.
E-mail addresses: roberts-brian-w@cooperhealth.edu (B.W. Roberts), Karagiannis-Paul@cooperhealth.edu (P. Karagiannis), colett58@rowan.edu (M. Coletta), Kilgannon-Hope@cooperhealth.edu (J.H. Kilgannon), Chansky-Michael@cooperhealth.edu (M.E. Chansky), Trzeciak-Stephen@cooperhealth.edu (S. Trzeciak).

http://dx.doi.org/10.1016/j.resuscitation.2015.03.015
0300-9572/

major regulator of CBF after cerebral injury, and derangements of $PaCO_2$ have been thought to worsen clinical outcomes after many forms of cerebral injury by altering CBF and increasing cerebral ischemia.[9–11] Hypocapnia has been postulated to be detrimental secondary to hypocapnia-induced cerebral vasoconstriction resulting in decreased CBF and increased cerebral ischemia potentially exacerbating cerebral injury.[9,12,13] The association between hypercapnia and poor outcome has been suggested to be secondary to hypercapnia-induced cerebral vasodilation and increased intracranial volume resulting in increased ICP and decreased cerebral perfusion, in addition to compounding acidosis, which often accompanies underlying disease processes.[10,14–16]

Cerebral injury is one of the most common reasons critically ill patients require initiation of mechanical ventilation.[17] During mechanical ventilation $PaCO_2$ levels are influenced by the prescribed ventilator settings initiated by the treating clinician. The effect of $PaCO_2$ management on clinical outcomes among patients with cerebral injury requiring mechanical ventilation remains unclear. Specifically, it is currently unclear if optimizing $PaCO_2$ can improve clinical outcome. If the available biomedical literature suggests that $PaCO_2$ optimization may attenuate acute cerebral injury in human subjects, this could serve as the scientific rationale for large-scale clinical trials of $PaCO_2$ optimization to improve clinical outcomes in patients suffering from acute cerebral injury.

The objective of this report was to systematically review and analyze the biomedical literature of clinical investigations testing the effects of $PaCO_2$ levels on clinical outcomes in human subjects suffering from acute cerebral injury. Our hypothesis was that hypocapnia and hypercapnia after acute cerebral injury is associated with poor clinical outcomes.

2. Materials and methods

2.1. Search strategy

We performed a search of Cochrane Library, PubMed, CINAHL, and other sources using the following search terms: *hypoventilation* or *hyperventilation* or *hypocapnia* or *hypercapnia* or *hypocarbia* or *hypercarbia*, and *brain injury* or *cerebral injury* or *head injury* or *ischemia* or *reperfusion* or *resuscitation* or *stroke* or *cerebral vascular accident* or *cardiac arrest*. We screened reference lists of all articles selected for inclusion to identify additional studies for potential inclusion. Finally, we consulted two independent experts in the field of critical care, to identify potential unpublished data. We planned to consider studies eligible for review regardless of language or publication type, and to have all foreign language studies translated to English as needed.

2.2. Study inclusion and exclusion criteria

We included all clinical studies of $PaCO_2$ management in patients who suffered cerebral injury requiring mechanical ventilation regardless of etiology of injury (e.g. traumatic brain injury, cerebral vascular accident, neonatal ischemic encephalopathy, post-cardiac arrest). Study inclusion criteria were as follows: (1) human subjects; (2) documented cerebral injury; (3) subjects required mechanical ventilation during the initial post-injury period; (4) documented measurement of $PaCO_2$; and (5) comparison of a clinical outcome measure (i.e. mortality, neurological outcome) between different $PaCO_2$ exposures (i.e. hypocapnia, normocapnia, hypercapnia) regardless of exposure definition (e.g. hypocapnia defined as $PaCO_2 < 35$ vs. <30 mmHg). We excluded studies that were secondary reports of previously published trials. We also excluded articles that were reviews, correspondence, or editorials; however, we screened the reference lists of review articles to identify further studies for inclusion.

2.3. Article selection and data extraction

Two reviewers (P.K. and M.C.) independently performed an initial relevance screen by reviewing the titles and abstracts of identified studies for potential eligibility. After the relevance screen, the two reviewers compared their logs, to identify any disagreement. In cases of disagreement, a third reviewer (B.W.R.) assessed the abstract, and a consensus was reached between the three reviewers. All studies deemed potentially relevant were obtained, and the full manuscripts reviewed for inclusion. The original two reviewers (P.K. and M.C.) independently extracted data on all patient populations, interventions, outcome measures, and results using a standardized data collection template. Any disagreements in these processes were resolved by consensus with a third reviewer (B.W.R.).

2.4. Study quality assessment

For all randomized control trials we assessed the quality of all included studies using Cochrane Collaboration's tool for assessing the risk of bias in clinical trials (Table 1)[18] As per the Cochrane Collaboration's tool for assessing the risk of bias in clinical trials, a high-quality study was defined as a grade of "A" in at least three of four methodology domains mentioned.[18]

Given the majority of the included studies were not randomized control trials we graded the quality of the non-randomized studies based on the Newcastle-Ottawa Scale (NOS) for assessing methodological quality or risk of bias in non-randomized studies as recommended in the Cochrane Handbook.[18] We customized the items in the NOS to the review question of interest (effects of hypocapnia and hypercapnia exposure on clinical outcome after cerebral injury) as described in Table 2. A high-quality study was defined as a grade of five stars (*).

2.5. Analysis

We performed a primarily qualitative analysis of the data in accordance with the recommended methodology for qualitative reviews published in the Cochrane Handbook.[18] In table format, stratified by individual publication, we collated and summarized the following: (1) etiology of cerebral injury [i.e. traumatic brain injury, cerebral vascular accident (ischemic and hemorrhagic), neonatal ischemic encephalopathy, and post-cardiac arrest syndrome]; (2) study design (i.e. retrospective, prospective observational, registry study, randomized control trial); (3) number of subjects in the different $PaCO_2$ exposure groups; (4) definition of $PaCO_2$ exposures (i.e. hypocapnia, normocapnia, hypercapnia); (5) timing of $PaCO_2$ measurements after initial cerebral injury; (6) effect of $PaCO_2$ exposures on outcome measures; and (7) study quality (defined above).

3. Results

3.1. Search and selection

The initial database searches identified 4555 potential articles. The majority of these studies were excluded (4456) during the relevance screening (Fig. 1). Studies were excluded during the relevance screening secondary to (1) $PaCO_2$ was not measured, (2) human subjects were not involved (i.e. animal models), (3) subjects did not have cerebral injury, or (4) subjects were not mechanically ventilated. A full manuscript review was performed on the remaining 99 papers, resulting in 17 papers included for final analysis with a total of 20,396 subjects. Table 3 displays the primary reasons for study exclusion.