Efficacy and safety of permissive hypercapnia in preterm infants: A systematic review

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Abstract

Context: In adults, permissive hypercapnia reduces mortality and ventilation duration. However, in preterm infants, findings from past research regarding the efficacy and safety of permissive hypercapnia are controversial. **Objective:** To evaluate the efficacy and safety of permissive hypercapnia versus normocapnia in preterm infants on mechanical ventilation. **Data Sources:** MEDLINE, EMBASE, CENTRAL, and CINAHL **Study Selection:** Published randomized controlled trials (RCTs), non-RCTs, interrupted time series, cohort studies, case-control studies, and controlled before-and-after studies were included. **Data Extraction:** Two reviewers independently screened the title and abstract and full text, extracted data, assessed the risk of bias, and evaluated certainty of evidence (CoE) according to the Grading of Recommendations Assessment, Development and Evaluation approach. A meta-analysis of RCTs was performed using the random-effects model. **Results:** Four RCTs (693 infants) and one cohort study (371 infants) were included. No significant differences existed between the permissive hypercapnia and normocapnia groups for bronchopulmonary dysplasia (BPD) (risk ratio [RR] 0.94; 95% confidence interval [CI] 0.74-1.18; very low CoE) and a composite outcome of death or BPD (RR 1.05; 95% CI 0.90-1.23; very low CoE). Permissive hypercapnia may increase necrotizing enterocolitis (RR 1.69; 95% CI 0.98-2.91; very low CoE), although the null or trivial effect cannot be excluded. No significant differences existed between the two groups for any other outcome assessed (very low-to-low CoE). **Limitations:** The sample sizes were less than the optimal sizes for all outcomes assessed, indicating the need for further trials. **Conclusions:** Permissive hypercapnia did not have any significant benefit or harm in preterm infants.

Introduction

Permissive hypercapnia is a mechanical ventilation strategy that tolerates the partial pressure of arterial carbon dioxide ($PaCO_2$) above the normal range (35–45 mmHg). This approach may protect the lung from volutrauma and barotrauma by modulating small tidal volumes and low peak inspiratory pressures. In adult patients with acute respiratory distress syndrome, mechanical ventilation with a low tidal volume using permissive hypercapnia decreased the mortality and duration of mechanical ventilation.[1-3]However, in pediatric or newborn patients, findings from previous reports on the effectiveness of this strategy are inconsistent and do not provide enough evidence of the safety profile.[4,5] In preterm infants, this approach is reported to cause a potential increase in the risk of intraventricular hemorrhage (IVH) due to permissive hypercapnia, which can result in neurodevelopmental impairment (NDI) because hypercapnia causes cerebral vasodilation and increases cerebral blood flow [6].Owing to controversial evidence on this topic, we conducted a systematic review and meta-analysis with an aim to examine the efficacy and safety of permissive hypercapnia, in comparison with the normocapnia strategy, in premature infants on mechanical ventilation.

Methods

The protocol of this systematic review was developed before the literature search and was registered at PROSPERO (CRD42020197204).

Selection Criteria for the systematic review

This systematic review included studies that compared the effectiveness of the two respiratory strategies (permissive hypercapnia versus targeting normocapnia) on mortality and morbidity in preterm infants on mechanical ventilation. All published randomized controlled trials (RCTs), non-RCTs, interrupted time series, cohort studies, case-control studies, and controlled before-and-after studies were eligible for inclusion in this review. Unpublished RCTs were eligible if sufficient information on risk of bias assessment was obtained. No language restrictions were applied, but the selected articles were required to have an English abstract. This systematic review excluded studies without sufficient data regarding the outcomes to be summarized, duplicate studies or data, and animal studies. Studies were excluded if they assessed only infants on noninvasive mechanical ventilation without intubation (e.g., those on continuous positive airway pressure [CPAP] or high-flow nasal cannula). Six important outcomes were selected a priori for assessment in this systematic review: (1) mortality at discharge from the neonatal intensive care unit (NICU) or at postmenstrual age of 36 weeks; (2) bronchopulmonary dysplasia (BPD), defined as oxygen use or respiratory pressure support [e.g., CPAP, high-flow nasal cannula at a rate of >2 L/min] at postmenstrual age of 36 weeks; (3) a composite outcome of death or BPD; (4) severe IVH (Grades III or IV of Papille's classification);[7] (5) cystic periventricular leukomalacia (cystic PVL); (6) necrotizing enterocolitis (NEC; Bell's criteria [?]2a)[8]; and (7) NDI (cerebral palsy, cognitive deficit, and vision or hearing impairment).

Search methods and strategy

A literature search was performed in the following databases from their inception to January 3, 2022: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Cumulative Index to Nursing and Allied Health Literature (CINAHL). A manual search of the reference lists of the review articles on this topic was conducted. Trial registrations of ClinicalTrials.gov, EU Clinical Trials Register, and Australian New Zealand Clinical Trials Registry were searched to check for ongoing trials. The literature search strategies included the following terms: population (newborn, infant or neonate and low birth weight, LBW, VLBW, ELBW or preterm, premature) and intervention (hypercapnia, carbon dioxide, CO_2). The full search strategy used for MEDLINE is presented in the supplementary material (Supplemental Table A).

Study selection and data extraction

Two reviewers (Y.O and F.M) independently screened the titles and abstracts of the selected articles derived from the literature search and reviewed the full text of all potentially relevant articles. Any discrepancy between the two reviewers was resolved by discussion first, and when it did not reach consensus, a third reviewer (T.I) adjudicated it.

Risk of bias assessment

The two authors (Y.O. and F.M.) independently assessed the risk of bias of the included studies for each outcome using the Revised Cochrane risk of bias tool for RCT (RoB 2.0) [9] and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized studies [10]. The following five domains of the risk of bias were assessed for RCTs: randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. Conflicts of assessment between the two reviewers were resolved through discussion, with the third reviewer (T.I.) adjudicated it, if needed.

Assessment of certainty of evidence and summary tables The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used to assess the certainty of evidence for each outcome across the studies. Certainty of evidence was categorized into four levels (high, moderate, low, or very low) and summarized in an evidence profile table. [11,12] As recommended by the GRADE approach, [11,13] certainty of evidence was preliminarily started as "high" for not only RCTs but also non-randomized studies because the risk of bias in non-randomized studies was assessed according to ROBINS-I on the same metrics as those of RCTs. [10] The certainty of evidence was downgraded for risk of bias, imprecision, inconsistency, indirectness, and publication bias. For assessing imprecision, the sample size required to detect a 20% risk

ratio [RR] reduction, called "optimal information sizes," was calculated using total event rates in the control groups of the included studies. [11,13]

Data synthesis and analysis

A meta-analysis was performed using the random-effects model with the Mantel-Haenszel method using Review Manager (RevMan), version 5.4 (The Nordic Cochran Center, The Cochrane Collaboration). The effect estimates were reported as RRs and absolute risk differences (ARDs) with 95% confidence intervals (95% CIs). Statistical significance was set at $p < 0.05$. Heterogeneity was assessed by visual inspection of the forest plot using the χ^2-test (significant if $p<0.10$) and I^2 statistic (heterogeneity considered significant if $I^2 > 40\%$). Subgroup analyses by gestational age (<28 gestational weeks, 28-32 gestational weeks), respiratory support (invasive ventilation or non-invasive ventilation), and age after birth (acute phase; 0-27 days, chronic phase [?] 28 days) were preplanned and performed.

Results

Search Results

Among the 3275 records identified in the initial literature search, 2336 were assessed for their title and abstract after the removal of duplicates (Figure A). The full text of 106 articles was assessed, and six articles were eligible for inclusion in this systematic review, which included 1074 preterm infants (four RCTs[14-17], one follow-up study of one RCT[18], and one cohort study[19]). The largest RCT was conducted in Germany, and all other studies were conducted in the USA. The included studies varied in the median gestational age (24.7–27.3 weeks), duration of permissive hypercapnia (24 hr to 14 days), and target CO_2 range (45–55 to 55–65 mmHg for the permissive hypercapnia group; 35–45 to 40–50 mmHg for the normocapnia group) as shown in Table 1. All studies used invasive mechanical ventilation, mainly intermittent positive pressure ventilation. The high-frequency oscillation mode was used only when necessary and was reported in two RCTs (Mariani 1999[14] and Thome 2015)[17].

Assessment of Risk of Bias

The overall risk of bias was low for most studies, except that the study by Thome (2006) [16] had a high overall risk of bias for BPD and NDI (Supplemental Table B). In the study by Thome (2006), the mortality in the permissive hypercapnia group was higher than that in the normocapnia group (36% vs. 19%). This can lead to a bias in the rates of BPD and NDI because those who died before the assessment of BPD or NDI could not have these outcomes. Owing to the characteristics of the intervention (targeting $PaCO_2$), care providers were not blinded in any of the included trials. BPD diagnosis that was made without an objective algorithm (e.g., oxygen reduction test) might be influenced by the outcome assessors' knowledge of the intervention assignment.[20] Therefore, the measurement outcome of BPD was considered to be concerning, to some extent, except for that reported in the study by Carlo (2002) [15], which used an algorithm for BPD diagnosis (Supplemental Table B).

Of note, the study by Carlo (2002) was terminated early because the infants treated with dexamethasone (another intervention of the RCT with a 2×2 factorial design) had high rates of NEC. Because the reason for early termination was not related to the comparison between permissive hypercapnia and normocapnia, we did not consider that it increased the risk of bias. For the cohort study of Hagen (2008) [19], the overall risk of bias was judged to be serious for IVH and NDI owing to concerns about remaining confounding and measurement outcomes (Supplemental Table C).

Effects of Interventions and Quality of the Evidence

Figure B show forest plots of the results of the meta-analysis of RCTs. The GRADE evidence profile table summarizes the assessment of the certainty of evidence for each outcome (Table 2). Mortality at discharge (or at a postmenstrual age of 36 weeks) was not significantly different between the two respiratory strategies (65/345 vs. 52/348; RR 1.26 [95% CI 0.91–1.75]; ARD 39 more per 1000 [95% CI 13 fewer to 112 more]; low certainty of evidence). The rates of BPD were not significantly different between the two respiratory

strategies (94/342 vs. 101/345, RR 0.94 [95% CI 0.74–1.18]; ARD 11 more per 1000 [95% CI 50 fewer to 86 more per 1000]; very low certainty of evidence). Notably, the largest RCT (Thome 2015) reported a significant increase in the rate of NEC with the use of permissive hypercapnia. In our systematic review, the difference in NEC rates between the groups was not significant; however, the estimated risk of NEC was higher in the permissive hypercapnia group than in the normocapnia group, with a lower boundary of 95% CI close to and just below 1.0 (32/345 vs. 19/348, RR 1.69 [95% CI 0.98–2.91]; ARD 38 more per 1000 [95% CI 1 fewer to 104 more per 1000, very low certainty of evidence]). An observational study (Hogan, 2008) reported no significant differences in IVH rates before NICU discharge and early childhood behavior or function scores at 2–3 years of age between the permissive hypercapnia and normocapnia groups.

Discussion

To our knowledge, this study is the first systematic review on this topic using the GRADE approach. It included four RCTs (693 infants) and one cohort study (371 infants) and demonstrated that permissive hypercapnia did not significantly reduce or increase any infants' outcomes assessed (death, IVH, BPD, NEC, PVL, and NDI) compared with the normocapnia strategy (very low-to-low certainty of evidence). However, the largest RCT (Thome 2015) [17] reported a higher rate of NEC in the permissive hypercapnia group than in the normocapnia group, which requires further investigation.

The strengths of our systematic review, compared with previous ones, include (1) the use of the GRADE approach to evaluate the certainty of evidence for each outcome, (2) the use of the definition of BPD at a postmenstrual age of 36 weeks, not at 28 days after birth, and (3) the inclusion of both RCTs and observational studies. The GRADE approach was developed as a transparent method for grading the certainty of evidence for systematic reviews and guidelines.[12] Although previous systematic reviews that evaluated the effect of permissive hypercapnia on BPD assessed the risk of bias in the included studies, they did not use the GRADE approach [12].

Unlike the previous systematic reviews that used BPD diagnosed at 28 days of age, this systematic review defined BPD as the use of oxygen or respiratory pressure support [e.g., CPAP, high-flow nasal cannula at a rate of >2 L/min] at 36 weeks of corrected gestational age.[21-23] Although defining BPD has been a controversial issue in recent years, the definitions or diagnoses near term or later (from 36 weeks to 40 weeks postmenstrual age or to 1 year of age) are considered better than those at 28 days or a month after birth because the former definitions predict long-term adverse consequences better than the latter.[24] The last systematic review on this topic (Ma, 2016) [21] reported that permissive hypercapnia did not reduce BPD (RR 0.93; 95% CI 0.83–1.03) (Ma 2016); however, the authors did not clearly describe the definition of BPD. Based on the results of that systematic review (Ma, 2016), the outcome of BPD seemed to include both BPD diagnosed at 28 days of age and that diagnosed at a postmenstrual age of 36 weeks together. Using the BPD definition at a postmenstrual age of 36 weeks, we found that hypercapnia did not reduce BPD. In addition to the small sample size, one of the other potential explanations for the negative finding for BPD is that permissive hypercapnia used might not always achieve low tidal volume enough to prevent BPD. However, none of the trials included in this systematic review measured and compared the tidal volumes of the two groups. All the included trials reported comparable peak inspiratory pressure (PIP) measurements between the two groups, except for one RCT (Thome 2015), which indicated that the target $PaCO_2$ level might be insufficient to achieve low PIP or small tidal volume enough to prevent BPD.

This systematic review found that permissive hypercapnia did not have significant adverse neurological effects (severe IVH and NDI), consistent with the findings of previous systematic reviews.[21,23] The increased risk of IVH due to permissive hypercapnia was also concerning in this review. High $PaCO_2$ and low pH dilate cerebral blood vessels, increase cerebral blood flow, and cause fluctuations in cerebral blood flow, which may predispose infants to IVH.[6,25, 26] Moreover, cerebral autoregulation was attenuated in the presence of hypercapnia. CO_2 cerebral blood flow reactivity is more robust than pressure flow [27] and there is a steep positive linear relationship between $PaCO_2$ and cerebral blood flow on postnatal days 2–4.[28] One potential reason for the lack of increase in IVH with permissive hypercapnia is that the target range of $PaCO_2$ in the permissive hypercapnia groups might be insufficient to increase IVH. One RCT (Mariani 1996) and one

cohort study included in this review used a target $PaCO_2$range of less than 55 mmHg in the permissive hypercapnia group. Moreover, in other studies, actual values of $PaCO_2$ did not exceed 55 mmHg despite the target $PaCO_2$, except in one study (Thome 2015). Even the Thome 2015 study did not achieve the target range in the permissive hypercapnia group, and the mean $PaCO_2$ exceeded 55 mmHg only after day 4. Therefore, it is possible that the actual $PaCO_2$ values of most infants in the permissive hypercapnia group did not reach the threshold (51–55 mmHg) that was reported to increase cerebral blood flow in previous studies. [28-31] . Another potential explanation for the lack of an increase in IVH is that most of the included studies administered sodium bicarbonate to correct acidosis. The correction of acidosis might attenuate the adverse effects of hypercapnia, although rapid infusion of sodium bicarbonate may increase the risk of IVH.[32, 33]

In this meta-analysis, the effect estimates (RR) indicated a potential increase in NEC in infants with permissive hypercapnia, although the difference was not statistically significant, with its 95% CI just crossing the neutral effect estimate (RR 1.69 [95% CI: 0.98–2.91]). Furthermore, the largest RCT (Thome, 2015) reported a significant increase in NEC in the permissive hypercapnia group. It is important to note that the RCT with an increased NEC in the permissive hypercapnia group (Thome 2015) used the longest intervention period (14 days after birth) and the highest target range of permissive hypercapnia ($PaCO_2$ of 65–75 mmHg) among all eligible studies. The effect of lengthy permissive hypercapnia with a high $PaCO_2$ target range on the NEC rates requires further investigation. An ongoing RCT aimed to enroll 160 preterm infants at <37 gestational weeks (HYFIVE; NCT02799875). The trial compares two different levels of target PCO_2 and pH (PCO_2 60–75 mmHg and pH[?]7.2 versus $PCO_2$40–55 mmHg and pH [?] 7.25) between 7 and 14 days in terms of outcomes such as alive ventilator-free days in 28 days, death, BPD, etc. This trial may provide further information on the optimal $PaCO_2$ level and period in preterm infants.

Our systematic review has several limitations. First, the sample sizes of the included studies did not reach the optimal information size for all outcomes assessed (Supplemental Table D). Therefore, the negative findings in the meta-analyses may simply be due to the insufficient sample size. This limitation was reflected in the certainty of evidence downgraded for imprecision. Second, there was clinical heterogeneity among the eligible studies, in which there was a wide variation in the range of targeted $PaCO_2$ and period for the interventions (permissive hypercapnia or normocapnia) (Table 1), although the statistical heterogeneity was low (I^2=0–28%). Lastly, the included studies were relatively old, and the findings of the studies may not be applicable to current clinical practice. In particular, respiratory management strategies for premature babies have been rapidly changing over the last decade, and non-invasive ventilation and non-invasive surfactant administration avoiding mechanical ventilation using an endotracheal tube are increasingly used.[34, 35] Therefore, infants who are on mechanical ventilation and are eligible for permissive hypercapnia may be sicker in the current clinical practice than those in previous trials.

Conclusion

Our systematic review found a low-to-moderate certainty of evidence that the permissive hypercapnia strategy neither provided any significant lung and neurodevelopmental benefits nor caused harm, such as IVH, PVL, and NEC. Because the sample size of this systematic review was insufficient for all the outcomes assessed, future studies are warranted.

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Figure legend

Figure A Abbreviations: CENTRAL, Cochrane central register of controlled trials; CINAHL, Cumulative index to Nursing and Allied Health Literature; RCT, randomized clinical trial

Figure B

The analyses were conducted using random effects models. Abbreviations: BPD, bronchopulmonary dysplasia; ; IVH, intra ventricular hemorrhage; NEC, necrotizing enterocolitis; NDI, neuro developmental impairment; PMA, postmenstrual age; PVL, periventricular leukomalacia;

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