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# Transcutaneous carbon dioxide monitoring for the prevention of neonatal morbidity and mortality (Review)

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# TABLE OF CONTENTS

[Intervention Review]

# Transcutaneous carbon dioxide monitoring for the prevention of neonatal morbidity and mortality

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## ABSTRACT

### Background

Carbon dioxide ($CO_2$) measurement is a fundamental evaluation in a neonatal intensive care unit (NICU), as both low and high values of $CO_2$ might have detrimental effects on neonatal morbidity and mortality. Though measurement of $CO_2$ in the arterial blood gas is the most accurate way to assess the amount of $CO_2$, it requires blood sampling and it does not provide a continuous monitoring of $CO_2$.

### Objectives

To assess whether the use of continuous transcutaneous $CO_2$ ($tcCO_2$) monitoring in newborn infants reduces mortality and improves short and long term respiratory and neurodevelopmental outcomes.

### Search methods

We used the standard search strategy of the Cochrane Neonatal Review group to search the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 11), MEDLINE via PubMed (1966 to November 1, 2015), EMBASE (1980 to November 1, 2015), and CINAHL (1982 to November 1, 2015). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.

### Selection criteria

Randomized, quasi-randomized and cluster randomized controlled trials comparing different strategies regarding $tcCO_2$ monitoring in newborns. Three comparisons were considered, that is, continuous $tcCO_2$ monitoring versus 1) any intermittent modalities to measure $CO_2$; 2) other continuous $CO_2$ monitoring; and 3) with or without intermittent $CO_2$ monitoring.

### Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group. Two review authors independently assessed studies identified by the search strategy for inclusion.

### Main results

Our search strategy yielded 106 references. Two review authors independently assessed all references for inclusion. We did not find any completed studies for inclusion, nor ongoing trials.

**Authors' conclusions**

There was no evidence to recommend or refute the use of transcutaneous $CO_2$ monitoring in neonates. Well-designed, adequately powered randomized controlled studies are necessary to address efficacy and safety of transcutaneous $CO_2$ monitoring in neonates.

## PLAIN LANGUAGE SUMMARY

**Transcutaneous carbon dioxide monitoring for the prevention of neonatal morbidity and mortality**

**Review question.** We reviewed the evidence about the effects of different modalities to monitor carbon dioxide ($CO_2$) in the newborn. Does the use of transcutaneous $CO_2$ monitoring improve survival and other important outcomes in newly born infants?

**Background.** $CO_2$ measurement is a very important procedure because abnormal values of $CO_2$ may have detrimental effects in the sick newborn. There are three main methods to assess $CO_2$: in the arterial blood gas, in the air exhaled from the body, and through the skin, that is, transcutaneously. The latter is minimally invasive and allows continuous monitoring. The evidence is current to November 2015.

**Study characteristics and results.** No studies were included in this review, and no ongoing studies were identified.

# BACKGROUND

## Description of the condition

Carbon dioxide ($CO_2$) measurement is a fundamental evaluation in a neonatal intensive care unit (NICU). Multiple factors may affect $CO_2$ production and consumption as well as changes in arterial partial pressure of $CO_2$ ($PaCO_2$). Normal ranges of $PaCO_2$ are described from 35 mmHg to 45 mmHg in healthy neonates. The optimal $CO_2$ values in ventilated infants have not been clearly defined (Woodgate 2001). Episodes of hypo- and hypercapnia (i.e. decreased and increased $PaCO_2$ levels, respectively) in intubated newborns are common (Van Kaam 2013). Importantly, both low and high values of $CO_2$ might have detrimental effects on neonatal morbidity and mortality. Thus, clinicians aim to maintain stable $CO_2$ values within the target range, for example, increasing ventilation in case of an increased $PaCO_2$ (Brouillette 1997). Assuring normocapnia (i.e. normal $PaCO_2$ levels) is essential in preterm infants, as this population is particularly vulnerable to lung and brain impairment. Retrospective studies have shown that episodes of hypocapnia are associated with a higher risk of developing bronchopulmonary dysplasia (BPD), germinal matrix and intraventricular hemorrhage (GMH-IVH), and cystic periventricular leukomalacia (PVL) in the preterm infant (Erickson 2002; Resch 2012). The mechanism presumed to cause BPD seems to be excessive volutrauma that promotes episodes of hypocapnia as highlighted by retrospective studies. Infants with hyaline membrane disease have reduced functional residual capacity and maximal lung volume. Thus excessive volutrauma is required to attain normocapnia. The inverse relationship between $PaCO_2$ and BPD was first described in 1987: the lowest incidence of BPD occurred in a centre using primarily continuous positive airway pressure (CPAP) ventilation with desired $PaCO_2$ levels of 55 mmHg to 60 mmHg (Avery 1987). Other studies found that a lowest $PaCO_2$ of less than 29 mmHg prior to exogenous surfactant was associated with an increased risk of BPD (Garland 1995; Kraybill 1989).

Since $CO_2$ is one of the main regulators of cerebral blood flow (CBF) (Ambalavanan 2001; Leahy 1980; Pryds 1989; Wyatt 1991), avoiding extremely low or high levels of $PaCO_2$ may be associated with reduction in neurologic morbidity rates (Bifano 1988; Collins 2001; Dammann 2001; Fabres 2007; Gannon 1998; Graziani 1992; Wiswell 1996). Hypocapnia causes cerebral vasoconstriction, decreased partial pressure of arterial oxygen, decreased oxygen release from hemoglobin (Laffey 2002) and excessive neuronal excitability due to increased oxygen demands (Victor 2005). Moreover, animal models of hypocapnia demonstrate nuclear DNA fragmentation (Fritz 2001; Fritz 2003), decreased levels of high energy phosphates, as well as neuronal (Fritz 2004) and mitochondrial alterations that lead to apoptotic cell death (Lasso Pirot 2007). Thus, low levels of $CO_2$ are associated with the development of PVL in ventilated preterm infants, potentially related to a decrease in CBF and subsequent ischemia (Ambalavanan 2001; Bifano 1988; Collins 2001; Dammann 2001; Gannon 1998; Graziani 1992; Wiswell 1996). On the other hand, high levels of $CO_2$ have been associated with an increased risk of GMH-IVH in very low birth weight (VLBW) infants as hypercapnia may generate vasodilation and increase in CBF (Wallin 1990). Therefore close monitoring of $CO_2$ levels, especially during the first days can be useful to prevent brain damage.

## Description of the intervention

The measurement of $CO_2$ in the arterial blood gas is the most accurate way to assess the amount of $CO_2$. However it requires blood sampling, thus increasing the need for blood transfusions. Moreover, it entails either arterial puncture (a painful procedure) or the placement of a central line (risk of infections). Therefore, alternative tools have been developed to measure $CO_2$ without blood sampling, such as end-tidal $CO_2$ and transcutaneous monitoring ($tcCO_2$). The latter has been shown to provide a more accurate estimate (Tobias 1997) in extremely preterm infants (Aliwalas 2005). The measurement of $CO_2$ on human skin was first described in 1960 (Severinghaus 1960), while the first commercially available $tcCO_2$ sensors were introduced twenty years later (Eberhard 1981). It is based on the fact that $CO_2$ gas diffuses through body tissue and skin and can be detected by a sensor at the skin surface. By warming the sensor, a local hyperemia is induced, which increases the supply of arterial blood to the dermal capillary bed below the sensor (Eberhard 2007). Precision of measurement is not affected by birth weight, site of transcutaneous probe application, mean blood pressure or mean arterial pressure (Aliwalas 2005). However, its use in the NICU might be complicated in some clinical situations, such as in cases of skin edema or hemodynamic instability (circulatory centralization). In addition, some technical limitations might affect $tcCO_2$ reliability. Sensor preparation, positioning, taping and repeated changes of the sensor location may limit its application (Molloy 2006). Precision of $tcCO_2$ is reduced in cases of very low or high $CO_2$ values, that is for low transcutaneous $CO_2$ the true $CO_2$ is higher than the measured transcutaneous $CO_2$; whereas for high transcutaneous $CO_2$ the true $CO_2$ is lower than the measured transcutaneous $CO_2$. Of note, this difference is not due to any systematic error in the equipment, but due to the natural behaviour of noisy data (Hejlesen 2009). Moreover, accuracy of intermittent $tcCO_2$ monitoring to obtain quick (less than five minutes) $CO_2$ readings has to be further investigated (Rauch 1999). Another important issue in the clinical setting concerns the temperature of the sensor of $tcCO_2$ because the precision of the reading might be affected by set temperature (Sørensen 2011) and higher temperatures of the sensor might be associated with skin lesions.

## How the intervention might work

Continuous monitoring allows for the possibility of prompt intervention in multiple clinical settings, such as mechanical ventilation (MV) settings, timing of extubation, need for reintubation, need for endotracheal (ET) suctioning, ET dislodgment and clinical worsening. Continuous monitoring may be useful in assisting clinicians to define a point of optimal ventilation during high frequency ventilation (Tingay 2013), as $CO_2$ changes may be rapid in this modality of ventilation. Similarly, $tcCO_2$ should be considered the preferred method of non-invasive $CO_2$ monitoring for neonatal transport (Tingay 2005), as infants with transcutaneous monitoring are more likely to have decreased ventilator peak pressures during transport and more likely to reach the tertiary centre with a more adequate pH and a $CO_2$ tension (O'Connor 1998). Trend monitoring of $tcCO_2$ might allow a timely diagnosis of acute pulmonary conditions, for example, air leak; it has been suggested that use of reference centiles of the trended

slopes of $tcCO_2$ might be used for automatic decision support (McIntosh 2000).

In addition to the mentioned advantages in guiding clinical decisions, the use of $tcCO_2$ might minimize the procedure of blood sampling for gas analysis, thus reducing the risk for anemia and the need for blood transfusions. More importantly, in the absence of a central line, $tcCO_2$ would avoid stressful stimuli due to heel lance. Of note, very recent studies highlight how early exposure to pain is associated with a modified cerebral structure studied with diffusion magnetic resonance imaging (MRI) in specific parts of the brain (Brummelte 2012). Moreover, higher numbers of skin breaks, especially in the first three weeks of life, are significantly associated with reduced white matter (WM) and subcortical grey matter maturation, where painful procedures are known to be associated with reduced noradrenaline/choline (Brummelte 2012). This impaired development of subcortical neurons (lower noradrenaline/choline) with secondary axonal changes in the WM might be involved in the mechanism of abnormal brain development. Of note, it has been suggested that neonatal procedural pain during the first weeks of life could be associated with delayed early postnatal body and head growth (Vinall 2012). In addition, older studies suggested that early neurological injury could be mediated by acute increases in heart rate, blood pressure, heart rate variability, intracranial pressure and decreased arterial oxygen saturation (Anand 1998). These physiological responses, due to their magnitude and rapidity, may cause reperfusion injury and venous congestion leading to GMH-IVH or PVL, or both. The diaphragmatic splinting associated with acute pain might lead to substantial changes in intrathoracic pressure, reflected in clinically significant alterations in intracranial blood volume and cerebral blood flow (Anand 1998).

### Why it is important to do this review

This review aims to assess the clinical utility of $tcCO_2$ monitoring. Importantly, levels of $CO_2$ are known to be able to affect short- and long term outcomes, with clinically relevant disturbances in both respiratory and neurological parameters. Moreover, $tcCO_2$ might support the clinician to optimize ventilation settings, timing of extubation and even to detect the need for intubation or clinical deterioration.

As far as we are aware, this is the first systematic review on $tcCO_2$ in neonates. It differs from *Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants* (Woodgate 2001). Firstly, the objective is to assess whether the use of a device ($tcCO_2$) might help the clinician to achieve the target $CO_2$, which might be either normocapnia, or permissive hypercapnia or other predefined values. Secondly, interventions might be compared with both an inactive ($tcCO_2$ versus other modalities to assess $CO_2$) and active control interventions (different modalities of $tcCO_2$, e.g. continuous versus intermittent use). Thirdly, the population might include both ventilated and non-ventilated infants.

## OBJECTIVES

1. To assess whether respiratory management guided by the use of continuous $tcCO_2$ monitoring versus any intermittent modalities to measure $CO_2$ (e.g. blood gas determinations, end tidal $CO_2$ or $tcCO_2$ monitoring itself) in newborn infants reduces mortality and improves short and long-term respiratory and neurodevelopmental outcomes.
2. To assess whether respiratory management guided by the use of continuous $tcCO_2$ monitoring versus other continuous $CO_2$ monitoring (i.e. continuous end tidal $CO_2$) in newborn infants reduces mortality and improves short and long term respiratory and neurodevelopmental outcomes.
3. To assess whether respiratory management guided by the use of continuous $tcCO_2$ associated with intermittent $CO_2$ monitoring (such as blood gas determinations or end tidal $CO_2$) versus continuous $tcCO_2$ without intermittent $CO_2$ monitoring in newborn infants reduces mortality and improves short and long term respiratory and neurodevelopmental outcomes.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled clinical trials, quasi-randomized controlled trials and cluster randomized controlled trials.

#### Types of participants

Newborn infants admitted to NICU, including any gestational and postnatal age, any birth weight, ventilated and non-ventilated, any ventilation modalities and any $CO_2$ target values.

#### Types of interventions

Respiratory management guided by the use of continuous $tcCO_2$ monitoring as in the following three comparisons.

1. Comparison 1: continuous $tcCO_2$ monitoring versus any intermittent monitoring. Continuous $tcCO_2$ might be used with or without intermittent $CO_2$ monitoring, such as blood gas determinations or end tidal $CO_2$ (see Subgroup analysis and investigation of heterogeneity);
2. Comparison 2: continuous $tcCO_2$ monitoring versus other continuous $CO_2$ monitoring (i.e. continuous end tidal $CO_2$);
3. Comparison 3: continuous $tcCO_2$ associated with intermittent $CO_2$ monitoring (such as blood gas determinations or end tidal $CO_2$) versus continuous $tcCO_2$ without intermittent $CO_2$ monitoring.

We consider brief interruption of $tcCO_2$ monitoring (e.g. in case of sensor preparation, repositioning, taping) as continuous use. Though the target $CO_2$ range might differ between trials, within each trial the $CO_2$ target range must be identical in both study groups.

#### Types of outcome measures

##### *Primary outcomes*

1. Bronchopulmonary dysplasia/chronic lung disease, defined as: respiratory support or oxygen, or both, at 28 days of life (NIH 1979)/ respiratory support or oxygen, or both, at 36 weeks of postmenstrual age (PMA) (Jobe 2001); physiological definition (Walsh 2004).

2. Death during initial hospitalization (all-cause mortality).
3. Major neurodevelopmental disability (cerebral palsy, developmental delay (Bayley or Griffith assessment more than two SD below the mean) or intellectual impairment (IQ more than two SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification) (Jacobs 2013).

***Secondary outcomes***

1. Pneumothorax diagnosed on chest X-ray (yes/no)
2. Need for mechanical ventilation in non-intubated infants (IPPV) (yes/no)
3. Duration of mechanical ventilation (IPPV; days)
4. Duration of respiratory support (IPPV or CPAP; days)
5. Duration of oxygen therapy (days)
6. Duration of hospital stay (days)
7. Retinopathy of prematurity: any and severe (stage 3 or greater) (ICROP 1984)
8. Necrotizing enterocolitis: any grade and requiring surgery
9. Need for blood transfusions (yes/no)
10. Each component of major neurodevelopmental disability will be evaluated as a secondary outcome:
11. a) cerebral palsy on physician assessment (yes/no); b) developmental delay or intellectual impairment: Bayley or Griffith assessment more than two SD below the mean or intellectual impairment (IQ more than two SD below mean); neuromotor development (Bayley Scales of Infant Development - Psychomotor Development Index (BSID PDI)) assessed in survivors; mental development (Bayley Scales of Infant Development - Mental Development Index (BSID MDI)) assessed in survivors; c) blindness vision (< 6/60 in both eyes); d) sensorineural deafness requiring amplification. We will report these components of this long-term outcome for all trials that have evaluated children after 18 months' chronological age. We will perform separate analyses for children aged 18 months to 24 months and aged three years to five years.
12. Cranial ultrasound abnormalities (yes/no): any GMH-IVH, grade 3 or 4 (IVH) according to Papile classification (Papile 1978) and cystic PVL
13. Brain MRI abnormalities (yes/no): moderate or severe abnormalities in the basal ganglia or thalamus, severe white matter lesions or abnormalities in the posterior limb of the internal; capsule assessed in the neonatal period (Rutherford 2010).

## Search methods for identification of studies

### Electronic searches

We used the criteria and standard methods of The Cochrane Collaboration and the Cochrane Neonatal Review Group. The full search strategies for each database are listed in Appendix 1.

We undertook a comprehensive search including:

- Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 7) in *The Cochrane Library*;
- MEDLINE (January 1996 to November 1, 2015);
- EMBASE (January 1980 to November 1, 2015);
- CINAHL (1982 to November 1, 2015);
- Abstracts of the Pediatric Academic Societies (PAS) from 2000 to 2015;
- Australian New Zealand Clinical Trials Registry (PSANZ) from 2005 to 2015.

We did not apply any language restrictions and searched the reference lists of any cited articles.

### Searching other resources

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; www.whoint/ictrp/search/en/).

## Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group. Each review author independently performed trial searches, assessed methodology and extracted data, and compared and resolved any differences found at each stage. We assessed methodology regarding blinding of randomization, intervention and outcome measurements, as well as completeness of follow-up (i.e. > 80%). We planned to use Cochrane standardized statistical methods. For categorical data, we planned to calculate the risk ratio (RR), absolute risk difference (RD), number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH). For continuous data, we planned to determine the mean difference (MD) and use 95% confidence interval (CIs).

### Selection of studies

Two review authors (OR, MB) independently searched and identified eligible trials that met the inclusion criteria. The review authors screened the titles and abstracts to identify potentially relevant citations. We planned to retrieve the full texts of all potentially relevant articles and independently assess study eligibility by completing eligibility forms designed in accordance with the specified inclusion criteria. We planned to review trials for relevance based on study design, types of participants, interventions and outcome measures. We planned to resolve any disagreements by discussion and, if necessary, by consulting a third review author (MGC). In the 'Characteristics of excluded studies' table we planned to cite the excluded trials along with the reasons for exclusion. We planned to contact the trial authors if the details of the primary trials were not clear.

### Data extraction and management

Two review authors (MB, OR) independently extracted data using a data extraction form developed ad hoc and integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group (EPOC) data collection checklist.

We planned to record the following characteristics from each included trial.

- Administrative details: author(s); published or unpublished; year of publication; year in which trial was conducted; details of other relevant papers cited.
- Details of the trial: study design; type, duration and completeness of follow-up (i.e. > 80%); country and location of study informed consent and ethics approval.
- Details of participants: sex, birth weight, gestational age and number of participants.

- Details of intervention: modality of use of $tcCO_2$ monitoring, type of $tcCO_2$ monitoring device, type of blood gas analyser, type of end tidal $CO_2$ device.
- Details of outcomes, as listed above.

We planned to resolve any disagreements by discussion between the review authors. We planned to describe any on-going trials identified, where available, detailing the primary author, research question(s), methods and outcome measures together with an estimate of the reporting date.

Where any queries arose or where we required any additional data, we planned to contact the trial authors. MGC planned to use Review Manager (RevMan) (RevMan 2014) to enter all the data.

### Assessment of risk of bias in included studies

Two review authors (SZ, MB) planned to independently assess the methodological quality of all included trials. We planned to assess the risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011a).

The items included for appraisal were:

1. selection bias: random sequence generation and selection bias, i.e.
   a. random sequence generation (biased allocation to interventions) due to inadequate generation of a randomized sequence;
   b. allocation concealment: selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment;
2. blinding of participants and personnel: performance bias due to knowledge of the allocated interventions by participants and personnel during the study;
3. blinding of outcome assessment: detection bias due to knowledge of the allocated interventions by outcome assessors;
4. incomplete outcome data: attrition bias due to amount, nature or handling of incomplete outcome data;
5. selective reporting: reporting bias due to selective outcome reporting;
6. other bias: bias due to problems not covered elsewhere in the table.

See Appendix 2 for more detailed description of risk of bias for each domain.

We planned to use a 'Risk of bias' graph to illustrate risk across trials. We planned to resolve any disagreements by consensus and, if necessary, by adjudication with a third review author (MGC).

#### *Quality of evidence*

We planned to assess the quality of evidence for the main comparison at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011a). This methodological approach considers evidence from randomized controlled trials as high quality that may be downgraded based on consideration of any of five areas: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. (Guyatt 2011a). The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades: 1) High: We are very confident that the true effect lies close to that of the estimate of the effect; 2) Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; 3) Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; 4) Very Low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect (Schünemann 2013).

We planned to independently assess the quality of the evidence found for outcomes identified as critical or important for clinical decision making. These outcomes include the three primary outcomes (bronchopulmonary dysplasia/chronic lung disease; death during initial hospitalization; major neurodevelopmental disability) as critical outcomes.

In cases where we considered the risk of bias arising from inadequate concealment of allocation, randomized assignment, complete follow-up or blinded outcome assessment to reduce our confidence in the effect estimates, we planned to downgrade the quality of evidence accordingly (Guyatt 2011b). We evaluated consistency by similarity of point estimates, extent of overlap of confidence intervals and statistical criteria including measurement of heterogeneity ($I^2$ statistic (Higgins 2003)). We planned to downgrade the quality of evidence when large and unexplained inconsistency across studies' results was present (i.e. some studies suggest important benefit and others no effect or harm without a clinical explanation) (Guyatt 2011d). We planned to assess precision accordingly with the 95% confidence interval around the pooled estimation (Guyatt 2011c). When trials were conducted in populations other than the target population, we planned to downgrade the quality of evidence because of indirectness (Guyatt 2011e).

We planned to enter data (i.e. pooled estimates of the effects and corresponding 95% confidence Interval) and explicit judgments for each of the above aspects assessed into the Guideline Development Tool, the software used to create 'Summary of Findings' (SoF) tables (GRADEpro GDT 2015). We planned to explain all judgements involving the assessment of the study characteristics described above in footnotes or comments in the SoF table.

### Measures of treatment effect

We planned to use the standard methods of the Cochrane Neonatal Review Group to synthesize the data. We planned to extract categorical data for each intervention group, and calculate RR and RD. We planned to obtain mean and standard deviation values for continuous data and perform analysis using the MD. For each measure of effect we planned to give the 95% CI and present NNTB and NNTH values, as appropriate.

### Unit of analysis issues

We planned to describe, for each included trial, the observations on participants at selected time points until their discharge from hospital. We planned to adjust for clustering by applying the intra cluster correlation coefficient if we included cluster trials.

### Dealing with missing data

We planned to obtain a drop-out rate for each trial. We planned to consider a drop-out rate that was equal to or greater than the event

rate of the control group as significant. If we found a significant drop-out rate, we planned to contact the study author(s) to provide additional data. We planned to perform a sensitivity analysis to evaluate the overall results, with and without the inclusion of trials with significant drop-out rate. If a study reports outcomes only for participants completing the trial or only for participants who followed the protocol, we planned to ask the study author(s) to provide additional information to facilitate an intention-to-treat analysis. Where this was not possible, we planned to perform a complete case analysis.

#### Assessment of heterogeneity

We planned to assess clinical heterogeneity by comparing the distribution of important participant factors between trials (e.g. age) and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). We planned to assess statistical heterogeneity by examining the $I^2$ statistic, a quantity that describes the proportion of variation in point estimates that is due to variability across trials rather than sampling error. We planned to interpret the $I^2$ statistic as described by Higgins 2003:

- < 25% no heterogeneity;
- 25 to 49% low heterogeneity;
- 50 to 74% moderate heterogeneity; and
- ≥ 75% high heterogeneity.

We planned also to evaluate the 95% CI for the $I^2$ statistic. In addition, we planned to employ a $Chi^2$ test of homogeneity to determine the strength of evidence that heterogeneity was genuine. We planned to explore clinical variation across trials by comparing the distribution of important participant factors among trials (e.g. age) and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type and co-interventions).

#### Assessment of reporting biases

We planned to assess publication bias using funnel plots if at least 10 clinical trials met our inclusion criteria (Egger 1997; Sterne 2011).

#### Data synthesis

We planned to summarize all eligible studies in RevMan 2014. We planned to use the standard methods of the Cochrane Neonatal Review Group to synthesize data using RR, RD, NNTB, NNTH, WMD and 95% CIs and use a fixed-effect model to perform a meta-analysis of the data from the included trials.

#### Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses regarding use of intermittent monitoring, gestational age, birth weight, sensor temperature of $tcCO_2$, type of $tcCO_2$ monitoring device, target of $CO_2$ (only if the same $CO_2$ target range is used within each study group), intubated versus not intubated, and type of ventilation.

**Comparison 1:** Continuous $tcCO_2$ monitoring versus any intermittent modalities to assess $CO_2$ (e.g. blood gas determinations, end tidal $CO_2$, or $tcCO_2$ monitoring itself).

- Continuous $tcCO_2$ with or without intermittent $CO_2$ monitoring (such as blood gas determinations or end tidal $CO_2$);
- Method of intermittent monitoring (blood gas determinations, end tidal $CO_2$, or $tcCO_2$ monitoring itself or a combined strategy).

**Comparison 2:** Continuous $tcCO_2$ monitoring versus other continuous $CO_2$ monitoring.

- Any continuous $tcCO_2$ with or without intermittent $CO_2$ monitoring (such as blood gas determinations or end tidal $CO_2$);
- Other method of continuous monitoring with or without intermittent $CO_2$ monitoring (such as blood gas determinations).

**Comparison 3:** Continuous $tcCO_2$ associated with intermittent $CO_2$ monitoring (such as blood gas determinations or end tidal $CO_2$) versus continuous $tcCO_2$ without intermittent $CO_2$ monitoring.

- Method of intermittent monitoring (blood gas determinations, end tidal $CO_2$, or $tcCO_2$ monitoring itself or a combined strategy).

**For all comparisons (1, 2 and 3):**

- Gestational age (with three subgroups, < 30 weeks, < 37 weeks, ≥ 37 weeks).
- Birth weight (with three subgroups, < 1500 g, < 2500 g, ≥ 2500 g).
- Sensor temperature of $tcCO_2$ (with two subgroups, < 42°C, ≥ 42°C). The temperature of the sensor of $tcCO_2$ is relevant for the following reasons: precision of the reading might be affected by set temperature; risk of skin lesions is likely to be increased for higher temperatures (Sørensen 2011).
- Type of $tcCO_2$ monitoring device.
- Target $CO_2$ (with three subgroups: 35 to 45 mmHg; 45 to 55 mmHg; > 55 mmHg), only if the same $CO_2$ target range is used within each study group.
- Intubated versus not intubated.
- Type of ventilation (with two subgroups, conventional or high frequency ventilation).

#### Sensitivity analysis

We planned to conduct sensitivity analyses to explore the effect of the methodological quality of the trials, checking if studies with a high risk of bias overestimate the effect of treatment.

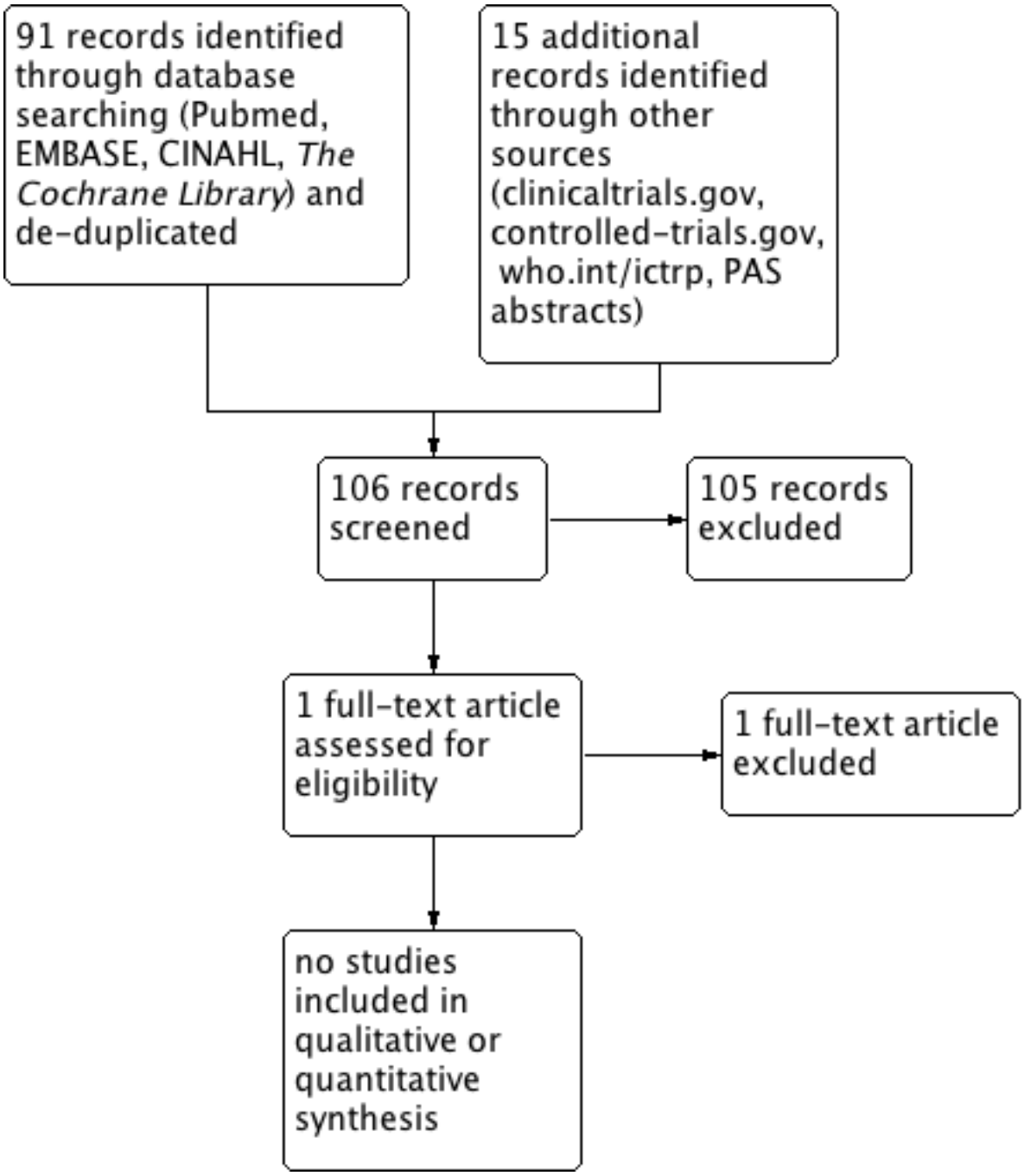
## RESULTS

### Description of studies

#### Results of the search

The literature search run in February 2015, and rerun in November 2015, identified 106 references (see Figure 1). After screening, only one study was considered as potentially eligible, but it was excluded (O'Connor 1998).

**Figure 1. Study flow diagram.**




### Included studies

We identified no trials that matched our inclusion criteria.

No relevant studies were found on the clinical trials registries for ongoing or recently completed trials.

### Excluded studies

We excluded the only potentially eligible study because there was no $PCO_2$ assessment in the control group and it was not clear whether $tcCO_2$ monitoring was continuous during the trial (O'Connor 1998), see Characteristics of excluded studies. The study was limited to transport and not ongoing management in the NICU. Newborns with $tcCO_2$ monitoring had lower ventilator peak pressures during transport and they had better pH and $PaCO_2$. The use of $tcCO_2$ monitoring was not associated with a longer stabilization time before transport.

## Risk of bias in included studies

No study met the eligibility criteria.

## Effects of interventions

No study met the eligibility criteria.

# DISCUSSION

## Summary of main results

We identified no eligible randomized controlled trials for inclusion that compared the use of continuous $tcCO_2$ monitoring versus any intermittent modalities to measure $CO_2$, continuous $tcCO_2$ monitoring versus other continuous $CO_2$ monitoring, or continuous $tcCO_2$ associated with intermittent $CO_2$ monitoring versus continuous $tcCO_2$ without intermittent $CO_2$ monitoring in newborn infants.

One study was excluded because it was limited to transport and not ongoing management in the NICU (O'Connor 1998). Interestingly, the use of $tcCO_2$ monitoring improved short-term respiratory outcome without increasing time for stabilization before transport.

We identified no ongoing trials.

## Overall completeness and applicability of evidence

We identified no eligible studies for inclusion.

## Quality of the evidence

We identified no eligible studies for inclusion.

## Potential biases in the review process

We used the standard methods of the Cochrane Neonatal Review Group for conducting this systematic review. Our inclusive search strategy would theoretically have included all relevant studies. We minimized any potential biases, though the choice of the criteria for considering studies for inclusion in this review (namely Types of interventions) led to the exclusion of one study that compared $tcCO_2$ monitoring with no monitoring (O'Connor 1998).

## Agreements and disagreements with other studies or reviews

Not applicable.

# AUTHORS' CONCLUSIONS

## Implications for practice

We did not find any studies that met our inclusion criteria and hence there is no evidence to recommend or refute the use of continuous $tcCO_2$ monitoring in neonates.

## Implications for research

Randomized controlled trials are necessary to evaluate the efficacy and safety of continuous $tcCO_2$ monitoring compared with any intermittent monitoring of $tcCO_2$, most importantly in the very preterm neonate. Moreover clinically relevant outcomes, such as bronchopulmonary dysplasia, intraventricular hemorrhage and periventricular leukomalacia, should be reported.

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We thank peer reviewer, Dr Georg M Schmölzer, for his additional advice.

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## CHARACTERISTICS OF STUDIES

### Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| O'Connor 1998 | O'Connor 1998 sought to determine the efficacy of transcutaneous carbon dioxide measurement during high-risk neonatal transport.<br><br>Excluded as study was limited to transport and not ongoing management in NICU. |

## APPENDICES

### Appendix 1. Search strategy

- CENTRAL in *The Cochrane Library*: transcutaneous AND (carbon dioxide) AND (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)
- MEDLINE: (transcutaneous AND ("carbon dioxide"[MeSH Terms] OR ("carbon" AND "dioxide") OR "carbon dioxide")) AND ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))
- EMBASE: (transcutaneous and carbon dioxide and (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) and (human not animal) and (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
- CINAHL: transcutaneous AND (carbon dioxide) AND (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
- abstracts2view.com/pasall/ of the Pediatric Academic Societies (PAS) from 2000 to 2015: "transcutaneous" AND "carbon dioxide" AND "newborn"
- clinicaltrials.gov; controlled-trials.com; www.whoint/ictrp/search/en/; and anzctr.org.au/ (PSANZ) from 2005 to 2015: transcutaneous AND "carbon dioxide" AND infant

### Appendix 2. Risk of bias tool

#### 1. Selection bias (Random sequence generation and allocation concealment)

For each included trial, we planned to categorize the risk of selection bias as:

##### *1a. Random sequence generation*

1. Low risk: the investigators describe a random component in the sequence generation process, such as referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, or minimization;
2. High risk: the investigators describe a non-random component in the sequence generation process (sequence generated by odd or even date of birth, sequence generated by some rule based on date or day of admission, sequence generated by some rule based on hospital

or clinic record number, allocation by judgment of the clinician, allocation by preference of the participant, allocation based on the results of a laboratory test or a series of tests, or allocation by availability of the intervention);
3. Unclear risk: no or unclear information provided.

***1b. Allocation concealment***

For each included trial, we planned to categorize the risk of bias regarding allocation concealment as:

1. Low risk: participant and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization), sequentially numbered drug containers or identical appearance, or sequentially numbered sealed opaque envelopes;
2. High risk: participant and investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on open random allocation schedule (e.g. a list of random numbers), unsealed or non-opaque envelopes, alternation or rotation, date of birth, or case record number;
3. Unclear risk - no or unclear information provided.

**2. Blinding (Performance bias)**

For each included trial, we planned to categorize the methods used to blind study personnel from knowledge of which intervention a participant received.

1. Low risk: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;
2. High risk: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key trial participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding;
3. Unclear risk - no or unclear information provided.

**3. Blinding (Detection bias)**

For each included trial, we planned to categorize the methods used to blind outcome assessors from knowledge of which intervention a participant received.

1. Low risk: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;
2. High risk: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding;
3. Unclear risk: no or unclear information provided.

**4. Incomplete outcome data (Attrition bias)**

For each included trial and for each outcome, we planned to describe the completeness of data including attrition and exclusions from the analysis.

1. Low risk:
   a. No missing outcome data;
   b. Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
   c. Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
   d. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
   e. For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
   f. Missing data have been imputed using appropriate methods.
2. High risk:
   a. Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
   b. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
   c. For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
   d. "As-treated" analysis done with substantial departure of the intervention received from that assigned at randomization;

e. Potentially inappropriate application of simple imputation.

3. Unclear risk: no or unclear information provided.

**5. Selective reporting (Reporting bias)**

For each included trial, we planned to describe how we investigated the risk of selective outcome reporting bias and what we found. We planned to access all the protocols of the included trials through clinical trials registries (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp) and direct contact with the trial authors.

We planned to assess the methods as:

- Low risk: the study protocol is available and all of the trial's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon);
- High risk: not all of the trial's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a trial;
- Unclear risk - no or unclear information provided (the study protocol was not available).

**6. Other potential sources of bias (Other bias)**

For each included trial, we planned to describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design used).

We planned to assess whether each trial was free of other problems that could put it at risk of bias as:

1. Low risk: the trial appears to be free of other sources of bias;
2. High risk: the trial has at least one important risk of bias (e.g. the trial had a potential source of bias related to the specific study design used or has been claimed to have been fraudulent or had some other problem);
3. Unclear risk: there may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias.

## CONTRIBUTIONS OF AUTHORS

MB and OR reviewed the literature and wrote the manuscript.

SZ and MGC assisted in the literature review and writing the manuscript.

LAR commented on and reviewed the manuscript.

## DECLARATIONS OF INTEREST

Matteo Bruschettini: no competing financial nor any other conflicts of interest
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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol. These will be applied to future updates if trials are included.

We changed 'continuous $tcCO_2$ monitoring' to 'Respiratory management guided by the use of continuous $tcCO_2$ monitoring' in two sections, Objectives and Types of interventions.

We searched the WHO trial registry, not noted in our protocol, for a more comprehensive search.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Carbon Dioxide; *Infant Mortality; Blood Gas Monitoring, Transcutaneous [*methods]; Morbidity

### MeSH check words

Humans; Infant; Infant, Newborn