BTS Guideline for diagnosing and monitoring paediatric sleep disordered breathing

Online Appendix 3 Question 3 Evidence Review and Protocol

Q3 For children undergoing investigation for sleep disordered breathing, does carbon dioxide monitoring with pulse oximetry improve clinical outcomes, when compared with pulse oximetry alone?

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Question Evidence Review

Q3 For children undergoing investigation for sleep disordered breathing, does carbon dioxide monitoring with pulse oximetry improve clinical outcomes, when compared with pulse oximetry alone?

Background

The addition of carbon dioxide (CO_2) monitoring to pulse oximetry for diagnosing sleep disordered breathing in children has major implications in terms of adding complexity and cost, but there are clinical situations when CO_2 monitoring may be of diagnostic value. This review will investigate if the addition of CO_2 monitoring to pulse oximetry improves clinical outcomes when compared to pulse oximetry alone.

Outcomes

Adherence to ventilation, changes to ventilation, quality of life, frequency of monitoring, requirement for more detailed sleep studies, hospital admissions and respiratory exacerbations.

Evidence Review

The initial literature search identified 17 studies of which six were deemed relevant. These included five retrospective cohort studies[1-5] and one prospective cohort study[6]. The definition of abnormal hypoventilation differed between the studies, so the definition used in each study is documented where relevant. One study used end tidal CO_2 monitoring[1] and five used a transcutaneous monitor[2-6]. The review also included studies where apnoea hypopnoea index (AHI) was used as a surrogate for pulse oximetry. Please note that due to a lack of direct evidence, diagnostic yield data was included in this review.

Adherence to ventilation

Adherence to ventilation was not reported in any of the studies.

Changes to ventilation

Two studies reported on changes to ventilation.[4,6] The first investigated children with achondroplasia and reported changes to ventilation in 1/30 patients when CO_2 monitoring was combined with pulse oximetry.[6] In the second study, the addition of CO_2 monitoring identified the need for ventilation changes in 13/29 children with neuromuscular disease and pre-existing restrictive lung defects.[4]

Both studies above[4,6] and three further studies[1,3,5] also investigated if the addition of CO_2 monitoring increased diagnostic yield. Two studies looked at the added value of CO_2 monitoring when abnormal pulse oximetry results were found[4,6] (Table 3a) and two reported the incidence of hypoventilation in patients where pulse oximetry was regarded as 'normal', but the definition of 'normal' oximetry varied between studies (Table 3b).[1,3] Diagnostic yield increased in all studies when CO_2 monitoring was added to pulse oximetry, but differences in result reporting between the studies did not allow meta-analysis or statistical analysis. A further study compared the added value of CO_2 monitoring in children with Down syndrome and healthy controls when abnormal AHI was recorded but statistical analysis was not undertaken (last row, Table 3b). Results showed no increase in the number of positive studies (OSA) in the Down syndrome group, but hypoventilation was detected in 18% of those with OSA (2 mild OSA, 1 moderate and 2 severe). One participant in the control group with severe OSA also had hypoventilation, but hypoventilation was not recorded in any participant with normal OSA. Although monitoring with CO_2 did not increase the number of participants reported as positive for OSA, it did provide further information for identifying patients with nocturnal hypoventilation.[5]

A final study reported on the correlation between CO_2 changes and partial obstruction in children with OSA. At sleep onset, greater increases in transcutaneous CO_2 ($TcCO_2$) were shown in children with OSA, which correlated with the duration of partial obstruction (measured using a Sonomat, a mat-based recording system for diagnosing SDB without the need for attaching sensors to the subject). An increase in CO_2 during REM sleep was also associated with increased partial upper airway obstruction, as reflected by a higher frequency of snoring or stertor.[2]

Table 3a: Comparison of sleep disordered breathing diagnostic yield and changes to ventilation between CO_2 and pulse oximetry monitoring and pulse oximetry monitoring alone

Study	Comorbidities	Definitions of Abnormal oximetry	Definitions of Abnormal CO_2	Results	(% patients)
Julliand 2012[6]	Achondroplasia	AI >1 / h AHI >5 / h Desat >5 / h Min SpO_2 <90%	PCO_2 >50mmHg >10%	Abnormal oximetry Abnormal oximetry + CO_2 Ventilation changes due to added CO_2 monitoring	90% 93% 3%
Trucco 2018[4]	NMD plus restrictive defect	<88% > 5 min	PCO_2 >50mmHg >25%	Abnormal oximetry Abnormal oximetry + CO_2 Ventilation changes due to added CO_2 monitoring	55% 100% 45%

AHI – apnoea hypopnoea index; AI – apnoea index; Desat – desaturation; NMD – neuromuscular disease

Table 3b: Summary of hypoventilation incidences in children with suspected sleep disordered breathing and 'normal' oximetry

Study	Comorbidities	Definitions of 'Normal' oximetry	Definitions of Abnormal CO_2	Hypoventilation (% patients)
Pautrat 2015* [3]	OSA / Lung disease / NMD	AHI <1.5 / h Min SpO_2 >90% Desat <1.4 / h	PCO_2 >50mmHg >25%, Peak $PtcCO_2$ >50mmHg, $PtcCO_2$ >50mmHg >2%, >10mmHg above waking	0% 2% 3% 2%
Carno 2009[1]	Obese / Non-obese	AHI <5	$P_{ET}CO_2$ >45mmHg >60%, PCO_2 >50mmHg >10%, Peak $P_{ET}CO_2$ >54mmHg	39%
Richard 2020[5]	Down syndrome Healthy controls	AHI <1	PCO_2 >50mmHg >25%	0% 0%

* Normal' oximetry is regarded as fulfilling all three criteria of normal oximetry; results are presented per abnormal CO_2 criteria

AHI – apnoea hypopnoea index; Desat – desaturation; NMD – neuromuscular disease; OSA – obstructive sleep apnoea; $PETCO_2$ mm partial pressure end tidal CO_2; PCO_2 – partial pressure CO_2; $PtcCO_2$ – partial pressure transcutaneous CO_2

Comorbidities

All studies included children with comorbidities in their cohorts, but only three studies assessed different subgroups within their populations.[1,3,5] Carno et al assessed the effects of obesity levels (based on body mass index (BMI) percentiles) on measured apnoea index (AI) and apnoea-hypopnoea index (AHI) levels and showed that AHI ≥5 was significantly higher in obese children when compared with overweight and normal children (p <0.05 for both) (Table 3c). The study also showed obstructive hypoventilation (defined as end-tidal capnography ($PETCO_2$) >45 mm Hg for >60% of total sleep time, >50 mm Hg for >10% of total sleep time, or a peak $PETCO_2$ of >54 mm Hg) in 12 subjects who had an AHI <5, but these were evenly distributed between the BMI percentile groups. Of these 12 subjects, one was <12 years old and 11 were >12 years old, suggesting that CO_2 monitoring was more useful in older subjects, but no statistical analysis was performed.[1]

Table 3c: Summary of abnormal pulse oximetry measurements in children with suspected sleep disordered breathing and differing levels of obesity

	% patients with			
Weight	**AI >1**	**AHI >2**	**AHI ≥5**	***p***
Normal (85 < BMI percentile)	52	79	44	NS*
Overweight (85 ≥ BMI percentile ≤ 95)	57	67	33	NS†
Obese (BMI percentile > 95)	48	88	74	<0.05‡

* No significance when compared with Overweight or Obese weight groups

† No significance when compared with Normal or Obese weight groups

‡ Significantly different to Normal and Overweight weight groups

AHI – apnoea hypopnoea index; AI – apnoea index; BMI – body mass index; NS – not significant

Pautrat et al classified patients into three groups: i) clinical suspicion of obstructive sleep apnoea (OSA); ii) restrictive or neuromuscular disease; or iii) lung disease. The OSA group was further subdivided into those with or without an underlying disease. Results showed no difference in the prevalence of hypoventilation for each of the four definitions (percentage of night time with a partial pressure transcutaneous CO_2 ($PtcCO_2$) >50 mmHg >25%, peak of $PtcCO_2$ >50 mmHg, percentage of night time with a $PtcCO_2$ >50 mmHg >2% and $PtcCO_2$ >10 mmHg above the morning awake minimal $PtcCO_2$ level) between the three patient underlying disease groups (chi-square test, p >0.05). Disease groups were also divided according to sleep disordered breathing severity (AHI <1.5, 1.5 ≥ AHI >5 and AHI ≥5), with the distribution of hypoventilation among the total population, or among the three groups not differing between AHI levels (chi-square test, p >0.05).[3]

Finally, Richard et al compared patients with Down syndrome (n=28) with controls (n=28) who were referred for a PSG for investigation of SDB. Results demonstrated that mean SpO_2 was lower (p=0,002) and $PtcCO_2$ was higher (p=0.001) in the Down syndrome group. CO_2 measurements also detected five patients with hypoventilation in Down syndrome group compared with one in the control group. Grouping participants by OSA severity also showed that in those with mild OSA group, $PtcCO_2$ and percentage total sleep time (%TST) with $PtcCO_2$ >50mmHg were higher in Down syndrome group, but no between group differences were found in $PtcCO_2$ between no, moderate or severe OSA.[5]

Quality of life, frequency of monitoring, requirement for more detailed sleep studies, hospital admissions and respiratory exacerbations

Quality of life, frequency of monitoring, requirement for more detailed sleep studies, hospital admissions or respiratory exacerbations were not reported in any of the studies.

Evidence statements

Based on limited evidence, the addition of carbon dioxide monitoring to pulse oximetry may identify more children with neuromuscular disease, Down syndrome and restrictive lung disease who would benefit from the initiation of non-invasive ventilation or adjustments to existing ventilator settings (**Ungraded**)

The addition of carbon dioxide monitoring to pulse oximetry may also increase the diagnostic yield of diagnosing sleep disordered breathing in children with neuromuscular disease, Down syndrome and restrictive lung disease when compared to pulse oximetry alone (**Ungraded**)

The addition of carbon dioxide monitoring to pulse oximetry does not appear to increase the diagnostic yield of diagnosing sleep disordered breathing in children without comorbidities, but it may provide additional diagnostic information for identifying patients with nocturnal hypoventilation **(Ungraded)**

Recommendations

- The addition of carbon dioxide monitoring to pulse oximetry should be considered for children with suspected sleep disordered breathing where hypoventilation is suspected, such as patients with

neuromuscular disease or patients suspected of central hypoventilation (e.g. congenital central hypoventilation syndrome) (**Conditional** – by consensus)

- Carbon dioxide monitoring should not be added to pulse oximetry for diagnosing sleep disordered breathing in children without comorbidities (**Conditional** – by consensus)

Good practice points

- ✓ If carbon dioxide measurements are not consistent with the clinical picture, this should be confirmed using a blood gas measurement. If using a transcutaneous carbon dioxide monitor, this should be recalibrated first. If the problem is not resolved, consideration should be given to checking and changing the sensor head membrane
- ✓ Pulse oximetry with CO_2 monitoring can be considered as a screening tool to identify hypoventilation in children with co-morbidities, or to assess response to adjustments to ventilatory settings in the home setting
- ✓ The American Academy of Sleep Medicine (AASM) recommends scoring as hypoventilation during sleep when >25% of the total sleep time as measured by either the arterial PCO_2 or surrogate (transcutaneous or end tidal which is more relevant in paediatrics) is spent with a PCO_2 >50 mmHg[7]

Research Recommendations

- Further research is needed into assessing if the addition of carbon dioxide monitoring to pulse oximetry improves patient/carer quality of life and patient clinical outcomes for children with suspected sleep disordered breathing when compared to pulse oximetry alone
- Further research is needed into assessing if the addition of carbon dioxide monitoring to pulse oximetry improves the diagnostic accuracy of diagnosing sleep disordered breathing in children with co-morbidities
- Research is needed into comparing the clinical benefits of the addition of end tidal carbon dioxide monitoring with pulse oximetry and transcutaneous carbon dioxide monitoring with pulse oximetry in children with suspected sleep disordered breathing

References

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4. Trucco F, Pedemonte M, Fiorillo C, et al. Detection of early nocturnal hypoventilation in neuromuscular disorders. *J Int Med Res.* 2018;46:1153-1161.
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7. Berry RB QS, Abreu AR, Bibbs ML, DelRosso L, Harding SM, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2.6. Darien, Illinois: American Academy of Sleep Medicine; 2020. Available at: <http://www.aasmnet.org/scoringmanual/> [Accessed 30 November 2021].

Question Protocol

Field	Content
Review Question	For children undergoing investigation for sleep disordered breathing, does carbon dioxide monitoring with pulse oximetry improve clinical outcomes, when compared with pulse oximetry alone?
Type of review question	Intervention review
Objective of the review	Adding CO_2 monitoring has major implications in terms of adding complexity and cost to the diagnostic process. We aim to investigate whether the addition of CO_2 estimation adds value to oximetry when trying to detect the presence or absence of sleep breathing disturbance. • Does the addition of CO_2 estimation lower the success rate of obtaining good data? • Do CO_2 values increase the number of positive studies? • Are there particular clinical situations when CO_2 adds diagnostic accuracy? • Are there particular thresholds of CO_2 that provide diagnostic value?
Eligibility criteria – population / disease / condition / issue / domain	Children (<17 years) with suspected sleep disordered breathing
Eligibility criteria – intervention(s)	Carbon dioxide monitoring AND pulse oximetry
Eligibility criteria – comparators(s)	Pulse oximetry alone
Outcomes and prioritisation	Adherence to ventilation Changes to ventilation Quality of life Frequency of monitoring Requirement for more detailed sleep studies Hospital admissions Respiratory exacerbations
Eligibility criteria – study design	Randomised controlled studies Prospective cohort studies Observational studies Superiority studies

Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Typically developing children <2 years Typically developing children 2-16 years Children with co-morbidities <2 years Children with co-morbidities 2-16 years
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 — Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler — Quality of evidence assessment Gradepro — Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews No date restriction
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)

Rationale / context – what is known	There is controversy as to whether CO_2 monitoring adds to diagnostic accuracy in sleep disordered breathing. It was omitted in the BTS neuromuscular guideline (Hull et al) owing to lack of evidence. There are clinical groups who might develop obstructive hypoventilation, which may not be detected accurately with oximetry alone; and as CO_2 monitoring adds complexity and cost, its use needs to be appraised.