A SYSTEMATIC REVIEW AND META-ANALYSIS OF PATIENT SAFETY OUTCOMES DURING PROCEDURAL SEDATION WITH AND WITHOUT CAPNOGRAPHY

Saunders RJK[1], Lightdale J[2], Pollock RF[3], Mestek M[4], Struys MMRF[5]

[1] Coreva Scientific GmbH & Co KG, Freiburg, Germany [2] UMass Memorial Children's Medical Center, Worcester, MA [3] Ossian Health Economics and Communications GmbH, Basel, Switzerland
[4] Medtronic Inc, Boulder, CO, USA [5]University of Groningen, Groningen, Belgium

Introduction
Robust evidence on the utility of capnography in patients undergoing procedural sedation (PS) has thus far been limited. Capnography can facilitate the early detection of alveolar hypoventilation and thereby prevent a "respiratory compromise cascade" in which untreated apnea may lead to desaturation, hypoxia, bradycardia, cardiac arrest and mortality. The aim of the present analysis was to conduct a systematic review and meta-analysis to establish whether the use of capnography significantly reduced adverse events during PS when used in addition to the current standard of monitoring.

Methods
A systematic literature review of PubMed, EMBASE and the Cochrane Library was conducted to identify randomized controlled trials (RCTs) of capnography versus standard monitoring published after January 1995. Endpoints of interest were desaturation (primary), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death. A random effects meta-analysis was conducted using RevMan 4.3.5 with outcomes reported as the odds ratios for capnography versus standard of care.

Results
After removal of duplicates, two reviewers independently screened 926 unique articles by title and abstract, leaving 21 articles for full-text review, of which 10 were excluded to leave 11 studies included in the meta-analysis. Monitoring techniques in the standard of care arm varied, but typically included pulse oximetry, blood pressure monitoring, and electrocardiography. Study heterogeneity (I2) was low across all endpoints studied. Six studies reported incidence of severe desaturation, all of which showed reductions with capnography relative to standard of care with pooled odds ratio (OR) was 0.51 in favor of capnography (95% confidence interval [CI] 0.39-0.66; p<0.00001; I^2 = 0%; Figure). Five studies reported the incidence of assisted ventilation during PS, all of which showed reduced need for bag-mask ventilation in the capnography arm relative to standard of care, although the pooled OR of 0.63 was not significant (95% CI 0.30-1.31, p= 0.22, I^2 = 0%). Incidence of bag-mask ventilation was 1.16% in control arms and 0.60% with capnography. We calculate that for a clinical trial to detect a statistical difference in these values would require over 8,400 patients to be enrolled. This rose to over 900,000 for an endpoint of major morbidity or mortality.

Conclusion
Use of capnography monitoring significantly reduced the incidence of mild and severe desaturation and showed a trend towards reducing the need for assisted ventilation in procedurally sedated patients undergoing surgery. Clinical trials to detect differences in more critical endpoints are likely to be unfeasible.

BACKGROUND

- Procedural sedation and analgesia (PSA) is the process by which a depression in level of consciousness and pain is pharmaceutically induced to ensure the comfort and cooperation of patients undergoing non-surgical procedures.
- Cardiopulmonary events associated with PSA typically stem from poor or absent ventilation, which can lead to a cascade of subsequent adverse events: the so-called respiratory compromise cascade (Figure 1).

AIMS

- The primary aim of the systematic review and meta-analysis was to establish whether capnography added to standard patient monitoring (pulse oximetry and visual inspection of ventilation) reduces the incidence of adverse events during PSA based on randomized controlled trials (RCTs) of patients undergoing a variety of surgical procedures.
- A secondary aim was to calculate the number of patients that would be required to demonstrate a reduction in patient harm

Figure 1. The respiratory compromise cascade

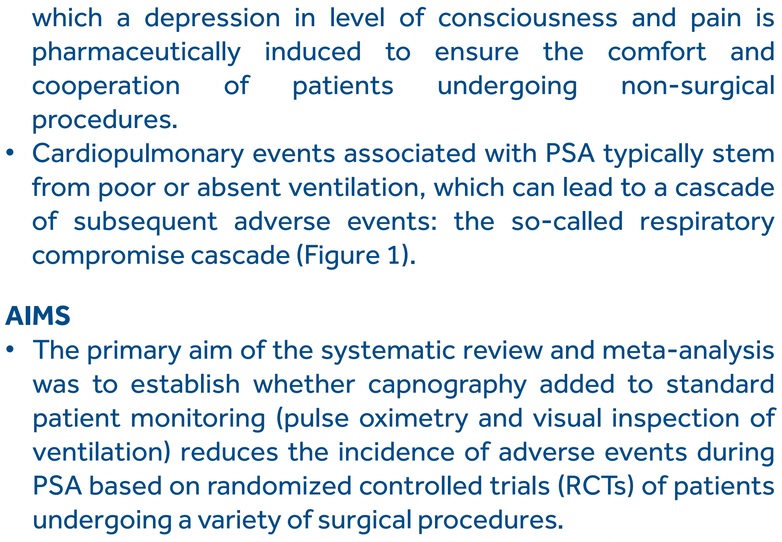
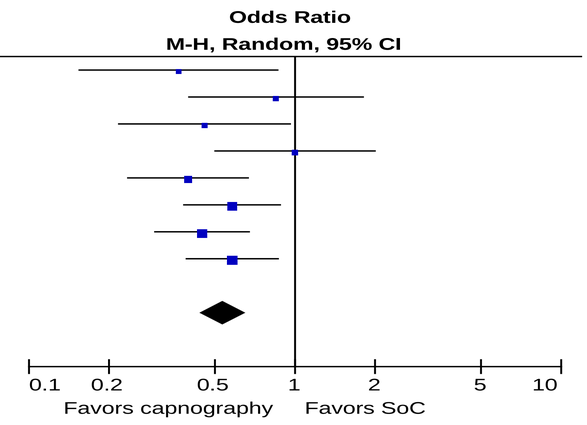


Figure 3. Random effects meta-analysis of mild desaturation

Study or Subgroup	Capnography Events	Capnography Total	Control (SoC) Events	Control (SoC) Total	Weight	Odds Ratio M-H, Random, 95% CI
Lightdale 2006	9	83	20	80	5.2%	0.36 [0.15, 0.86]
Slagelse 2013	13	263	16	277	6.7%	0.85 [0.40, 1.80]
Deitch 2010	17	68	27	64	6.9%	0.46 [0.22, 0.96]
Langhan 2015	23	77	23	77	7.9%	1.00 [0.50, 1.99]
Qadeer 2009	57	123	85	124	13.2%	0.40 [0.24, 0.67]
Zongming 2014	42	341	70	359	19.3%	0.58 [0.38, 0.88]
Friedrich-Rust 2014	47	267	86	266	20.0%	0.45 [0.30, 0.67]
Beitz 2012	48	383	74	374	20.9%	0.58 [0.39, 0.86]
Total (95% CI)		**1605**		**1621**	**100.0%**	**0.54 [0.44, 0.66]**
Total events	256		401			

Heterogeneity: Tau² = 0.01; Chi² = 7.88, df = 7 (P = 0.34); I² = 11%
Test for overall effect: Z = 6.05 (P < 0.00001)



CI, confidence interval; M-H, Mantel-Haenszel; SoC, standard of care

- Harm was defined as either:
  - Severe morbidity or mortality, in a prospective clinical trial of capnography versus visual assessment with pulse oximetry
  - Requirement for assisted (bag-mask) ventilation

METHODS

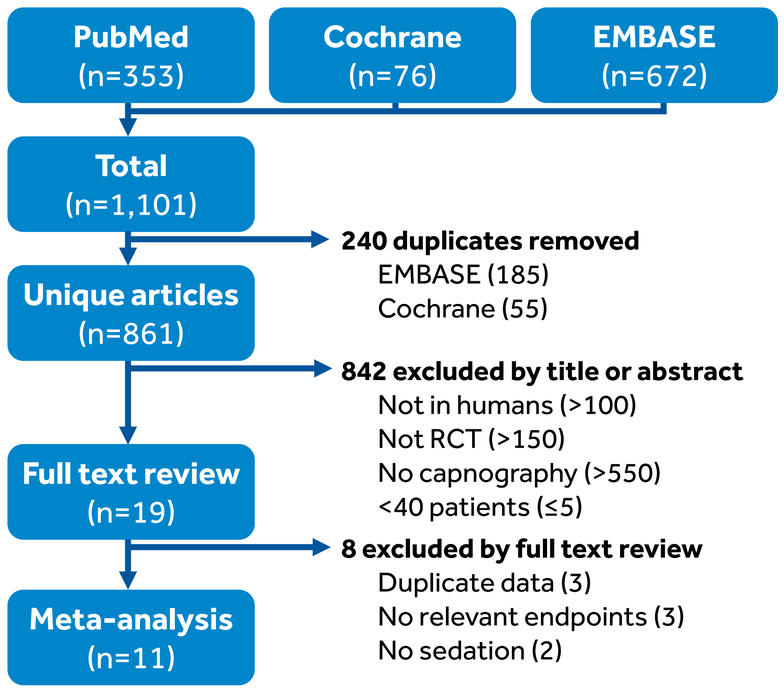
Systematic literature review

- Literature searches were conducted in PubMed, the Cochrane Library and EMBASE using Medical Subject Heading (MeSH) terms and title and abstract free-text searches.
- Sourcerer was used for bibliography management and literature screening.[1]
- Searches identified RCTs in patients receiving sedation during ambulatory surgery and in which visual assessment of ventilation and pulse oximetry monitoring (SoC) was compared with SoC plus capnography.
- Searches were limited to studies indexed between January 1, 1995 and June 17, 2015 (the search date)

Meta-analysis

- Data extraction, initial data consolidation and summary statistics were performed in Microsoft Excel. Data for each endpoint were subsequently entered into Review Manager 5.3.4 for results synthesis.[2]
- Endpoints were oxygen desaturation/hypoxemia (primary endpoint), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA.
- Heterogeneity of data was evaluated using Chi^2 and I^2 statistics presented by Review Manager 5.3.4.
- Study quality was assessed using a modified Jadad scale (0-8). Studies scoring >5 were designated high quality.
- Mean intervention effect across all eligible studies was calculated using (after analysis of heterogeneity) a random effects model as described by DerSimonian and Laird.[3] An estimate of between-study variation was calculated by the Mantel-Haenszel methodology.[4] Outcomes were reported as pooled mean odds ratios (OR) with 95% confidence intervals (CI).

Figure 2. Base case results



RESULTS

- Literature searches identified 1,101 articles, of which 240 were duplicates, leaving 861 articles for title and abstract screening. After independent screening by two reviewers, 19 studies were left for full-text review. 11 were included in the meta-analysis (Figure 2).[5-15]
- Eight studies scored >5 in the quality assessment.[5,6,8-13]
- All studies reported mild desaturation, although definitions varied from an oxygen saturation (SpO_2) of <95% to <90% for ≥15 seconds
- In the primary analysis (n=8), there was little heterogeneity (I^2 = 11%) and the mean OR of 0.54 (95% CI 0.44–0.66) was consistent for random- and fixed-effects models (Figure 3).
- Capnography significantly reduced incidence of mild and severe desaturation, and apnea relative to the standard of care (Table 1)
- Assisted ventilation, supplemental oxygen, bradycardia and hypotension showed non-significant differences (Table 1).
- Sensitivity analyses in exclusively adult patients, in studies using moderate sedation only, and in all studies (n=11) showed that the meta-analysis outcomes were robust to changes in the subsets of studies used for data synthesis.

Table 1. Odds ratios based on high-quality studies

Event	n	OR with capnography relative to SoC	95% confidence interval
Mild desaturation	8	0.54	0.44-0.66
Severe desaturation	3	0.49	0.34-0.71
Assisted ventilation	4	0.54	0.25-1.16
Apnea	2	0.49	0.32-0.75
Supplemental oxygen	5	0.83	0.59-1.17
Bradycardia	3	1.23	0.87-1.74
Hypotension	4	1.03	0.74-1.43

Randomized, controlled trial requirements

- The RCT size to detect statistically significant differences between two monitoring modalities was calculated using [16]
- The incidence of bag-mask ventilation was 1.16% with SoC and 0.60% with capnography. An RCT to detect this difference would need to enroll over 8,400 patients
- For mortality and severe morbidity, 27,726 patients would need to be enrolled if a 50% reduction in event incidence (from 0.33%) is assumed
  - A 10% reduction would require >900,000 patients.

CONCLUSIONS

- Capnography monitoring was associated with statistically significant reductions in apnea, and mild and severe oxygen desaturation.
- Reduction in events early in the respiratory compromise cascade may increase patient safety with respect to later events
- RCTs powered to provide direct links between use of monitoring and a reduction in patient harm may not be feasible.

ACKNOWLEDGMENTS

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