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# PATIENT SAFETY DURING PROCEDURAL SEDATION USING CAPNOGRAPHY MONITORING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

### Objective

To evaluate the effect of capnography monitoring on sedation-related adverse events during PSA administered during ambulatory surgery relative to visual assessment and pulse oximetry alone.

### Design and Setting

Systematic literature review and random effects meta-analysis of randomized controlled trials (RCTs) reporting sedation-related adverse event incidence when adding capnography to visual assessment and pulse oximetry in patients undergoing PSA during ambulatory surgery in the hospital setting. Searches for eligible studies published between 1995 and 2015 (inclusive) were conducted in PubMed, the Cochrane Library and EMBASE without any language constraints. Searches were conducted in June, 2015.

### Interventions

Capnography monitoring relative to visual assessment and pulse oximetry alone.

### Primary and Secondary Outcome Measures

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA.

### Results

The literature search identified 861 unique articles, of which 11 were ultimately included in the meta-analysis. Addition of capnography to visual assessment and pulse oximetry was associated with a significant reduction in the incidence of apnea (OR 0.49, 95% CI 0.32–0.75), as well as mild (OR 0.54, 95% CI 0.44–0.66) and severe (OR 0.49, 95% CI 0.34–0.71) desaturation. Reduced occurrence of assisted ventilation was also observed with capnography, but this did not reach significance.

**Conclusions**

Meta-analysis of 11 RCTs published between 2006 and 2015 showed a reduction in respiratory compromise during PSA with the inclusion of capnography monitoring. In particular, use of capnography was associated with less mild and severe oxygen desaturation, and may help to avoid the need for assisted ventilation.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

**Strengths**

- The studies included in the analysis were all published in 2006 or later, representing modern medical practice and providing consistent evidence of improvements in patient safety with the use of capnography monitoring.
- The study findings further substantiate a previously-published meta-analysis, which found that capnography monitoring was more likely to detect adverse events.

**Limitations**

- The level of sedation employed in each study was not uniformly reported, resulting in a mixture of different sedation levels in the primary analysis and precluding an analysis of outcomes by sedation level.
- As with all meta-analyses, the study findings may be affected by publication, search or selection bias affecting the studies ultimately included in the analysis; however, where possible, steps were taken to minimize the effects of bias on the analysis, but the degree to which these steps were successful is difficult to quantify.

## BACKGROUND AND AIMS

The administration of procedural sedation and analgesia (PSA) involves achieving a drug-induced depression in level of consciousness and pain to ensure the comfort and cooperation of patients undergoing non-surgical procedures. Significant adverse events associated with PSA are relatively rare but not inconsequential, and can include severe oxygen desaturation, bradycardia, hypotension, and cardiac arrest.[1,2] Consensus dictates that levels of sedation are directly related to patient risk during PSA, as is the potential for unintended progression from moderate to deep sedation.[3] Generally speaking, most cardiopulmonary events associated with PSA stem from poor or absent ventilation cascading into hypoxia, tissue injury and cardiac decompensation (Supplement, Figure 3). In turn, maintaining patient safety involves the identification of respiratory compromise to prompt the use of clinical intervention before further complications occur.[4,5,6,7,8,9]

In current clinical practice, patient monitoring during PSA often relies on visual assessment of ventilation and use of pulse oximetry, which reflects hypoxemia.[10,11,12,13,14] To date, a mandate to include capnography in patient monitoring, as a means of early detection of alveolar hypoventilation, has remained a topic of debate.[15] In particular, there has been a perceived gap between various study outcomes and evidence of improved patient safety. No studies have provided "hard proof" that addition of capnography to patient monitoring may reduce severe morbidity and mortality during PSA (in part because of ethical considerations to ensure patient rescue), and efforts to use meta-analysis to determine the utility of capnography to identify clinically significant respiratory depression have been faulted for large heterogeneity and non-standard endpoints.[16,17]

The primary aim of the present systematic review and meta-analysis was to understand whether capnography added to patient monitoring only (consisting of pulse oximetry and visual inspection of ventilation) reduces the incidence of adverse events during PSA based on randomized controlled trials of patients undergoing a variety of surgical procedures. As a secondary aim, a power calculation was performed to determine the number of patients that would be required to demonstrate a reduction in

patient harm, defined as severe morbidity or mortality, in a prospective clinical trial of capnography versus visual assessment with pulse oximetry. The analysis was based on the hypothesis that earlier and more sensitive detection of ventilatory changes with capnography may allow for more timely intervention and prevention of potential adverse events, such as cardiac dysrhythmias. Throughout the analyses, we sought to provide the highest level of synthesized evidence with respect to the clinical utility of capnography monitoring during PSA. To mitigate potential pitfalls due to non-standard endpoints, particular emphasis was placed on maintaining a consistent definition of adverse events across all studies included.

## METHODS

Literature searches were conducted in PubMed, the Cochrane Library and EMBASE. Search terms were a combination of Medical Subject Heading (MeSH) terms and free-text searches within the articles title and abstract. Searches aimed to identify all literature reporting on randomized, controlled trials in patients receiving sedation during ambulatory surgery and in which visual assessment of ventilation and pulse oximetry monitoring (control) was compared with control plus capnography. No review protocol was registered in advance, but the full search strategy (Supplement, Table 3) and further details are provided in the Supplement. Only articles or abstracts published on or after January 1, 1995 were included and all searches were performed on June 17, 2015. No language exclusion was applied and inclusion was not dependent on the capnography monitor in use. After duplicate removal, title and abstract screening (Supplement, Table 4) was performed independently by RS and RFP. Full-text versions of all non-excluded articles were retrieved by MM and reviewed independently by RS and RFP. Data were then extracted independently by RS and RFP into data extraction forms in Microsoft Excel (Microsoft Corporation, Redmond, WA). Any discrepancies in the extracted data were resolved by reference to the original study, reaching consensus between RS and RFP. All extracted endpoint data were reviewed by JL and MMS for clinical utility to ensure that all synthesized data relate to

clinically equivalent endpoints. Extracted data included the number of patients with events and the population at risk, in addition to items required to assess article quality and bias.

**Endpoints**

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA. The protocol was left open for the analysis of other patient safety endpoints that were reported by ≥3 studies. Cardiac arrest and death were considered to be representative of severe morbidity and mortality.

**Quality and potential bias**

Assessment of article quality was conducted on a study (as opposed to outcome) level using a modified Jadad scale,[18] with additional criteria added to make the adaptation specific to monitoring. The Jadad scale scores articles on their design (randomized and blinded) and their reporting (all patients accounted for), with a maximal score of 5 (high quality) and a low score of 0 (low quality). Additional data included here were endpoint definitions, patient population, hospital location at which patients underwent sedation, and the staff responsible for monitoring. In keeping with Jadad, items related to trial design could score up to twice as highly as items relating to trial reporting. The reporting of the inclusion/exclusion criteria and endpoint definitions scored one point each, and reporting the location of sedation, and the monitoring staff scored half-point point each, making the maximal score 8 (high quality). For the purposes of analyzing study quality, studies with scores of 0–5 were considered to be low quality, while studies scoring 5.5–8 were designated as high quality studies.

Risk of bias in results was evaluated through the declaration of funding sources and conflicts of interest. If the study was funded by industry then the study scored 2, any conflicts of interest declared relating to industry funding outside of the current research publication scored 1. A study with low potential for bias, therefore, would have a score of 0. A high potential for bias was defined as a score of 3, while a score of 1–2 was considered to indicate moderate potential for bias.

### 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.[19] Heterogeneity of data was evaluated using $Chi^2$ and $I^2$ statistics presented by Review Manager 5.3.4. The meta-analysis performed calculated the mean intervention effect across all eligible studies using (after analysis of heterogeneity) a random effects model as described by DerSimonian and Laird.[20] An estimate of between-study variation was provided by the Mantel-Haenszel methodology.[21] The outcome reported for each endpoint is the pooled mean odds ratio (OR) and its 95% confidence interval.

For sensitivity analyses, the tested conditions were: (1) inclusion of only moderate sedation, (2) inclusion of only studies with low risk of bias, (3) inclusion of only studies based in the US, (4) inclusion of only studies based in Europe, (5) exclusion of pediatric data, (6) exclusion of gender-specific studies, (7) exclusion of data in patients <30 years of age.

### Patient involvement

No patients, service users, carers or lay people were involved in the design or conduct of this study. Outcome measures were all related to patient safety during PSA, but were not developed based on an explicit elicitation of patient priorities, experience, and preferences.

## RESULTS

Literature searches of PubMed, the Cochrane Library and EMBASE returned 353, 76, and 672 articles, respectively. After removal of 240 duplicates (55 Cochrane, 185 EMBASE), 861 articles remained for abstract screening. Although reasons for exclusion varied (Supplement, Table 4), the two independent reviewers agreed upon a total of 19 articles to be retained for full-text review (Cohen's kappa, 1.0). Eight articles were excluded on full-text review (Supplement, Figure 4) because they: reported duplicate data (n=3), did not report patient safety data (N=3), and did not include sedation (n=2). The

11 articles included for analysis are presented in Table 1. All studies reported desaturation endpoints, although the definition did vary by study (Supplement, Table 5). Other endpoints were heterogeneously reported, but were in most cases reported by ≥3 studies making meta-analysis feasible. Results reported are from random-effects models unless otherwise stated. Results for hypotension and use of supplemental oxygen are provided in the Supplement.

**Mild desaturation**

All studies reported mild desaturation, with the definition varying from an oxygen saturation ($SpO_2$) of <95% to <90% for ≥15 seconds. In the primary analysis of high quality studies (n=8), there was little evidence of heterogeneity ($I^2$ = 11%) and the mean OR did not differ between random-effects and fixed-effects models. Results indicated that capnography significantly reduced the incidence of mild desaturation (OR = 0.54, 95% CI 0.44–0.66; Figure 1). As such, a mild desaturation event is approximately half as likely to occur if capnography monitoring is used, compared with no use of capnography. If all available data were included (Supplement, Figure 5), there was evidence of significant heterogeneity ($I^2$ = 49%) with an OR of 0.65 (95% CI 0.51–0.81). Using exclusively studies with equivalent definitions of mild desaturation (<90%, n=6), evidence of heterogeneity ($I^2$ = 47%) is still present. The OR estimated from these studies was 0.60 (95% CI 0.46–0.77).

**Severe desaturation**

Six studies, of which three were classified as high quality, reported severe desaturation. All bar one of the studies defined severe desaturation as $SpO_2$ </≤85%. The primary analysis for this endpoint returned an OR of 0.49 (95% CI 0.34–0.71), further supporting the significant reduction in desaturation incidence with the inclusion of capnography (Figure 1). As with mild desaturation, there was no evidence of heterogeneity in the three high-quality studies ($I^2$ = 0%) and the OR was consistent between random-effects and fixed-effects models.

Synthesizing estimates from all available data supported the primary analysis (Supplement, Figure 6), the OR was reduced by 0.02 and the confidence interval tightened (OR 0.47, 95% CI 0.34–0.66). There

was no significant heterogeneity between studies ($I^2$ = 16%). Focusing on the five studies reporting an endpoint of SpO2 </≤85%, there was no heterogeneity and the OR was estimated at 0.44 (95% CI 0.32–0.60). Overall, results support a greater than 50% reduction in the incidence of severe desaturation events if capnography monitoring is used.

**Apnea**

Apnea was less widely reported or reported in combination with disordered respiration. Comparable endpoints were reported by four studies, of which two were high quality. Primary analysis demonstrated a significant reduction in apnea with capnography monitoring (OR 0.49, 95% CI 0.32–0.75), with no evidence of heterogeneity (Supplement, Figure 7). If all studies were included the degree of heterogeneity became significant ($I^2$ = 75%) and the outcome lacked significance at the 5% level (OR 0.75, 95% CI 0.43–1.33). The degree of between study heterogeneity supported the use of a random-effects model, analysis using a fixed effects model did not change the estimated OR but did restrict the 95% CI to 0.57–0.99. The difference between the primary and secondary analyses for this endpoint was driven by the study of Kochhar et al., which found apnea to be increased in the capnography arm.

**Bradycardia**

Three studies, all of high-quality, reported bradycardia outcomes. Its definition (heart rate <50 beats/minute) was consistent among trials and there was no evidence of between study heterogeneity ($I^2$ = 0%). In all studies, the incidence of bradycardia was higher in the capnography arm compared with the control arm (Supplement, Figure 8). Overall, capnography monitoring was associated with a non-significant increase in bradycardia (OR 1.23, 95% CI 0.87–1.74).

**Assisted ventilation**

Only one study reported one instance of what they termed "respiratory failure," that was treated with assisted bag-mask ventilation. In contrast, the number of studies reporting assisted and/or bag-mask ventilation was sufficient to perform a meta-analysis of this endpoint as a surrogate for respiratory

failure. In total, five studies reported this and all were classified as high-quality. The primary analysis returned no evidence of heterogeneity and an OR of 0.83 (95% CI 0.59–1.17). In every case, the need to provided assisted ventilation was lower in the capnography arm compared with the control arm (Figure 2). The lack of significance reflects the low number of observed events and the subsequent potential for error.

**Sensitivity analyses**

A series of sensitivity analyses were conducted in which the studies included in the estimation of the OR were varied. The results of these analyses are presented in Table 2 and show that results are generally robust to the studies included for data synthesis. There were limited data available to assess the impact of capnography monitoring during moderate sedation. Data available indicate that the impact of capnography is reduced relative to deep sedation. With respect to severe desaturation events, there was also a substantial difference between US and European data. In Europe, addition of capnography monitoring was estimated to reduce the incidence of severe desaturation by about 40%. For the US based studies this increased to 65%, meaning that almost 2 in 3 severe desaturation events were avoided.

Patient safety concerns often focus on mortality and severe morbidity. There was no evidence that these outcomes differ between control and capnography arms in the present meta-analysis. The incidence of these events during nurse-administered PSA has been reported to be 1 event per 303 procedures (0.33%).[22] Taking this value and using the assumption that capnography could prevent 50% of events, the formula provided by Zhong (2009) to calculate the trial size required to demonstrate statistical superiority returned 27,726 patients.[23] Switching to an assumption that capnography would prevent 10% of events, the required trial size was calculated to be >900,000 patients.

## DISCUSSION

The findings of a meta-analysis of recent RCTs comparing visual assessment of ventilation and pulse oximetry monitoring with and without capnography during PSA showed that the incidence of apnea and oxygen desaturation events were significantly reduced with the use of capnography. Other endpoints that could be affected by capnography monitoring were also considered and the majority was found to be associated with substantial, but not significant, benefits to patient safety. Specifically, and of potential clinical importance, was the consistency of data across multiple high-quality clinical trials reporting a reduced incidence of assisted ventilation with capnography monitoring. No endpoints assessed in the meta-analysis indicated significant patient safety concerns with capnography. In addition, sensitivity analyses suggested that a clinical trial designed to test for a significant difference in patient harm with use of capnography would require an unfeasibly large number of patients. Not only is the feasibility of performing such a superiority trial low, but meta-analyses such as the present study, are not able to detect this difference from the relatively small number of existing lower-powered studies currently available in peer-reviewed medical literature.

The analysis is timely given the ongoing lively debate as to whether the addition of capnography to patient monitoring during PSA adds value.[17] Without doubt, potential technical and financial burdens have further limited adoption of capnography monitoring in various clinical settings.[15,17] Nevertheless, it is important to recognize that patient safety benefits may offset a number of these concerns if the outcomes are applicable to current medical practice.[24] In this regard, the 11 trials identified in the present analysis were all relatively recent, with the first published study identified in 2006. The data used in the meta-analysis therefore represents modern medical practice, and provides consistent evidence of improvements in patient safety with the use of capnography monitoring.

These findings further substantiate a previously published meta-analysis (Waugh *et al.*), which found that capnography monitoring was more likely to detect adverse events, but was faulted for large endpoint heterogeneity.[16] In the present meta-analysis, we focused on identifying high-quality studies,

and on maintaining consistent definitions across all included studies, thereby minimizing potential for heterogeneity. The results show that the addition of capnography to patient monitoring during PSA results in increased patient safety, with significant reductions in apnea, as well as mild and severe levels of oxygen desaturation.

More recently, a meta-analysis by Conway *et al.* reported a significant benefit with capnography during colonoscopy only with respect to hypoxemia. However, the study identified and screened only a fraction of the literature included in the present analysis (388 papers in Conway *et al.*, compared with 861 papers in the current study) and retrieved fewer randomized controlled trials (6 versus 11). In addition, Conway *et al.* excluded two trials in which an independent observer monitored capnography output for all patients, and signaled to the attending physician when respiratory compromise was identified with capnography either immediately (intervention) or after a specified delay (control).[5,6] The rationale for this was to prevent unnecessary patient harm while avoiding investigator bias. Based on our understanding, the two trials that Conway and colleagues excluded are, contrary to expectation, the only studies in the literature that could be considered fully blinded. Among the other studies, the attending physician would have been aware of study arm assignment.[32,38,42] The results of the Conway analysis should therefore be interpreted with caution. Nevertheless, the finding of consistent outcomes for hypoxemia in Conway *et al.* (relative risk 0.59, 95% CI 0.48 to 0.73) and mild desaturation in the present analysis (OR 0.54, 95% CI 0.44 to 0.66; RR 0.65, 95% CI 0.57 to 0.74) was encouraging. These findings are also aligned with a European randomized, controlled trial of capnography that was published after the analysis was complete.[25]

Yet another ongoing debate in PSA concerns the clinical importance of seemingly minor endpoints, such as mild desaturation (oxygenation <90% for 15 seconds). Although such endpoints may be transient and perhaps clinically insignificant, several recent studies have suggested that mild desaturation, as a common intraoperative event, may have an impact on post-surgical outcomes.[26] For example, one retrospective study determined that patients who experienced perioperative hypoxemia/desaturation had a significant increase in their length of hospital stay (+2.0 days,

p<0.0001).[27] The long-term importance of these endpoints in terms of patient outcomes and quality of life remains unknown.

Over all of the studies included in the analysis, there were no reports of patient mortality. Only the largest trials reported any requirement for assisted/bag-mask ventilation, which is used as an intervention and thereby a proxy measure for potentially life-threatening events. Although it is generally accepted that much larger studies would be useful to assess whether or not capnography monitoring impacts patient major morbidity and mortality, there has been no determination of the trial size that would be required. Power calculations suggest such a large randomized controlled trial is likely to be impractical.

For healthcare providers, the most significant finding may be the consistency of data surrounding apnea and severe oxygen desaturation, as well as reduced need for assisted ventilation with capnography. Two closed claim reviews both found that inadequate oxygenation/ventilation was the most frequent event leading to a claim related to PSA outside the operating room.[28,29] The potential cost burden is demonstrated by the median cost of a claim settled being USD 330,000 (in 2007 USD).[28] The authors reported that better monitoring would have reduced the number of claims.[28] A similar message was returned following the fourth National Audit Project in the UK, which analyzed major complications of airway management in the National Health Service and determined that capnography monitoring could have led to earlier identification of airway obstruction, potentially preventing 74% of death or neurological injury cases.[30,31] Studies included in the present meta-analysis reported that disordered ventilation as detected by capnography preceded desaturation events by 30 to 60 seconds.[32]

The meta-analysis did find an increase in bradycardia with capnography monitoring that was non-significant, but consistent among the three included studies reporting the endpoint. However, in each of the three trials, patients in the capnography arm had larger doses and increased use of multiple agents for inducing PSA. Such confounding is plausible, and may not be unusual. In a non-blinded study published after the present analysis, the authors identified increased incidence of hypotension

in the capnography arm, in addition to higher sedative doses, patient ASA class, and incidence of comorbidities.[33] All other findings of the current analysis were in line with expectations around the potential benefits of capnography. Earlier identification of respiratory compromise appears to result in more timely intervention and prevention of its escalation into patient harm.

As with all data synthesis projects, the present study is only as accurate and reliable as the data underlying it. In the literature, there are examples of newly-published clinical trials that do not align with the results of published meta-analyses, and meta-analysis results changing on the publication of new data.[34,35] The systematic nature of study identification and inclusion criteria in the present analysis was designed to identify all available literature and provide the most robust estimates of intervention effect. However, the included studies came from a variety of hospital settings, in which the rate of patient safety events might vary. Analyses for particular settings were undertaken, but were then limited by reduced data availability. In total, this analysis represented 4,083 patients (control 2,053 and Capnography 2,030) over 11 studies. Between trials, the number of patients enrolled varied between 132 and 757. Notably, only the four studies including >500 patients identified rare outcomes, such as differences in use of assisted ventilation.

## CONCLUSIONS

The results of this comprehensive meta-analysis of high-quality clinical trials provide clear and consistent evidence of decreased respiratory compromise when capnography monitoring is used during procedural sedation and analgesia (PSA). Specifically, the analysis identified a statistically significant and clinically meaningful reduction in apnea, as well as in mild and severe oxygen desaturation. Large, well designed, randomized controlled trials to provide direct links between use of capnography and reduction in patient harm may not be feasible. In turn, calls for this type of primary evidence may delay adoption of capnography monitoring during PSA as a valuable tool for early intervention and improved patient safety.

**Word Count** 3,572

## AUTHOR CONTRIBUTIONS

MM formulated the research question; RFP and RS devised the search strategy and data extraction protocol, which was critically reviewed and revised by MM, JRL and MMRFS; RFP and RS then conducted the literature searches, screening, data extraction, and meta-analysis, and co-wrote the manuscript; MM, JRL and MMRFS critically reviewed the manuscript and made substantive revisions prior to submission.

## DATA SHARING STATEMENT

All data used to derive the outcomes presented in the study are documented in the manuscript and supplementary materials. No additional data are therefore available.

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## TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## ETHICAL APPROVAL

No ethical approval was required for the study as all data were derived from published data; neither animal nor human subjects were enrolled as part of the present study.

## FUNDING AND STUDY SPONSOR ROLE

This study was funded by Medtronic plc following a research proposal submitted by Ossian Health Economics and Communications GmbH. The sponsor reviewed the final manuscript prior to submission, but submission was not contingent on a particular outcome of the analysis.

## FINANCIAL AND COMPETING INTEREST DISCLOSURE

All authors have completed the Unified Competing Interest forms at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

- Michael Mestek is a full-time employee of Medtronic plc.
- Richard Pollock is a full-time employee of Ossian Health Economics and Communications GmbH, which received research and consultancy fees from Medtronic plc. to conduct the literature review and meta-analysis and prepare the manuscript.
- Rhodri Saunders was a full-time employee of Ossian Health Economics and Communications GmbH at the time of performing the meta-analysis and is currently a director of Coreva Scientific GmbH & Co. KG.
- Michel MRF Struys's research group/department received grants and funding from The Medicines Company (USA), Masimo (USA), Fresenius (Germany), Acacia Design (The Netherlands), Medtronic (USA) and honoraria from The Medicines Company (USA), Masimo (USA), Fresenius (Germany), Baxter (USA), Medtronic (USA), Demed Medical (Belgium).
- Jenifer R. Lightdale has served as a consultant for Medtronic and Norgine, and has received speaker honorarium from Mead-Johnson and Perrigo.

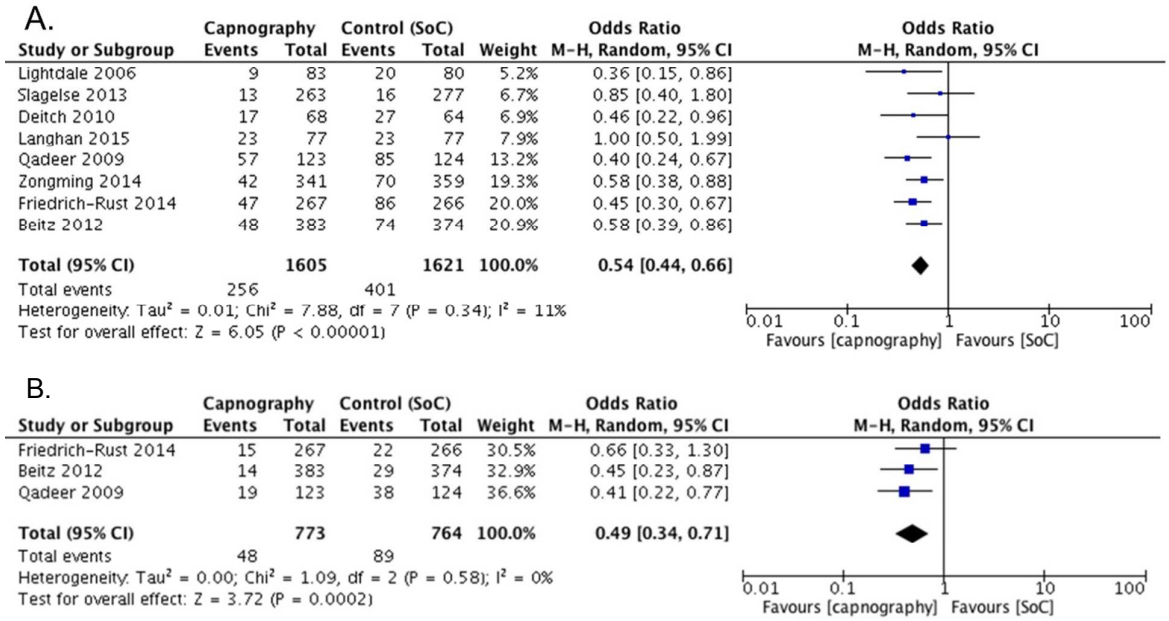
## TABLES AND FIGURES

**Table 1 Included studies reporting endpoints of interest**

| Study (reference) | Country | Trial dates | Modified Jadad | Potential for bias | Hospital setting | Depth of sedation | Sedative | N (control, Cap) |
|---|---|---|---|---|---|---|---|---|
| Beitz 2012[36] | Germany | Feb-10, Jan-11 | 5.5 | High: 3 | Colonoscopy | "adequate" | Propofol | 757 (374, 383) |
| Deitch 2010[37] | US | Nov-06, Feb-08 | 5.5 | Low: 0 | Emergency department | Moderate | Propofol | 132 (64, 68) |
| Friedrich-Rust 2014[38] | Germany | Jun-12, May-13 | 6 | Low: 0 | Colonoscopy | Deep | Propofol+ | 533 (266, 267) |
| Kochhar 2015[39] | US | NA | 3.5 | Low: 0 | EGD | Moderate | Opioid and BZP | 210 (108, 102) |
| Langhan 2015[40] | US | Sep-11, Jan-13 | 6 | Low: 0 | Pediatric emergency department | NA | Ketamine, midazolam | 154 (77, 77) |
| Lightdale 2006[6] | US | Dec-03, Nov-04 | 8 | Low: 0 | Endoscopy | Moderate | Fentanyl, midazolam | 163 (80, 83) |
| Mehta 2014[41] | US | NA | 3.5 | Low: 0 | Colonoscopy | Moderate | Opioid and BZP | 232 (115, 117) |
| Qadeer 2009[5] | US | Jan-07, May-08 | 7.5 | Moderate: 1 | ERCP and EUS | NA | Midazolam+ | 247 (124, 123) |
| Slagelse 2013[42] | Denmark | Sep-10, Jan-11 | 6 | No: 0 | Endoscopy | NA | Propofol | 540 (277, 263) |
| van Loon 2014[32] | Netherlands | Apr-10, Jan-11 | 5 | No: 0 | Gynecology | Deep | Propofol | 415 (209, 206) |
| Zongming 2014[43] | China | Nov-10, May-13 | 6 | No: 0 | Abortion | Deep | Propofol | 700 (359, 341) |

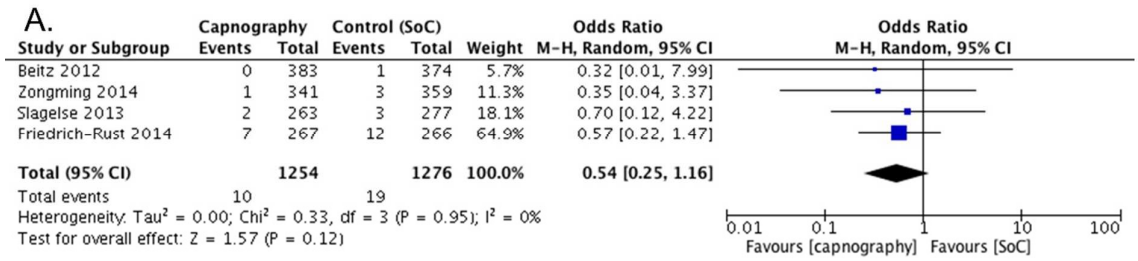
+, in combination with multiple other agents; BZP, benzodiazepine; Cap, Capnography (arm); EGD, Esophagogastroduodenoscopy; ERCP, Endoscopic retrograde cholangiopancreatography; EUS, Endoscopic ultrasonography

**Figure 1** **Mild and severe desaturation are reduced with capnography monitoring**




The odds ratios for the mild desaturation endpoint are presented for high-quality studies (primary analysis) for mild desaturation (A) and severe desaturation (B). CI, Confidence interval; M-H, Mantel-Haenszel

**Figure 2** **Need for assisted ventilation is consistently reduced with capnography monitoring**




The odds ratios for the assisted ventilation endpoint are presented for high quality studies (primary analysis, A), which were also all the studies with data. CI, Confidence interval; M-H, Mantel-Haenszel

**Table 2 Sensitivity analyses around the primary analyses, treatment effect is the odds ratio [95% confidence interval]**

| Scenario | Desaturation, mild | Desaturation, severe | Apnea | Bradycardia | Hypotension | Assisted ventilation | Supplemental oxygen |
|---|---|---|---|---|---|---|---|
| **Base case (high quality studies)** | **0.54 [0.44, 0.66]** | **0.49 [0.34, 0.71]** | **0.49 [0.32, 0.75]** | **1.23 [0.87, 1.74]** | **1.03 [0.74, 1.43]** | **0.54 [0.25, 1.16]** | **0.83 [0.59, 1.17]** |
| All studies with data | 0.65 [0.51, 0.81] | 0.47 [0.34, 0.66] | 0.75 [0.43, 1.33] | 1.23 [0.87, 1.74] | 1.03 [0.74, 1.43] | 0.54 [0.25, 1.16] | 0.93 [0.65, 1.33] |
| Moderate sedation | 0.67 [0.44, 1.04] | – | 0.92 [0.52, 1.64] | – | – | – | – |
| US only | 0.64 [0.44, 0.93] | 0.35 [0.21, 0.59] | 0.75 [0.43, 1.33] | – | – | – | 0.82 [0.27, 2.54] |
| Europe only | 0.65 [0.52, 0.81] | 0.61 [0.40, 0.93] | – | 1.46 [0.70, 3.03] | 0.95 [0.64, 1.40] | 0.57 [0.25, 1.29] | 0.91 [0.63, 1.30] |
| Studies with potential bias excluded | 0.69 [0.58, 0.82] | 0.51 [0.28, 0.90] | 0.92 [0.52, 1.64] | 1.46 [0.69, 3.08] | 0.95 [0.64, 1.41] | 0.56 [0.25, 1.23] | 1.12 [0.81, 1.55] |
| Studies in pediatrics excluded | 0.64 [0.54, 0.75] | 0.47 [0.34, 0.66] | 0.79 [0.38, 1.65] | 1.23 [0.87, 1.74] | 1.03 [0.74, 1.43] | 0.54 [0.25, 1.16] | 0.90 [0.63, 1.31] |
| Gender-specific studies excluded | 0.60 [0.50, 0.72] | 0.45 [0.31, 0.63] | 0.75 [0.43, 1.33] | 1.23 [0.87, 1.74] | 1.02 [0.71, 1.48] | 0.57 [0.25, 1.29] | 0.83 [0.59, 1.17] |
| Studies with mean age >30 years | 0.59 [0.49, 0.70] | 0.49 [0.33, 0.74] | 0.79 [0.38, 1.65] | 1.23 [0.87, 1.74] | 1.03 [0.74, 1.43] | 0.54 [0.25, 1.16] | 0.80 [0.57, 1.14] |

CI, confidence interval; OR, odds ratio; US, United States

# SUPPLEMENT

## METHODS: Literature screening and data extraction

All returned articles were consolidated in a database (Sourcerer, Covalence Research Ltd, London UK), and duplicate studies were removed. Title and abstract screening using criteria detailed in (Supplement, Table 4) was performed independently by RS and RFP. Full-text versions of all non-excluded articles were retrieved by MM and reviewed independently by RS and RFP using the inclusion criteria in Table 4 (Supplement). Data were extracted from all articles included after abstract and full-text review. Extracted data included the number of patients with events and the population at risk, in addition to items required to assess article quality and bias. This was performed independently by RS and RFP and checked by ME and MMS. All extracted endpoint data were reviewed by JL and MMS for clinical utility. The aim was to ensure that all synthesized data relate to clinically equivalent endpoints

## RESULTS: Hypotension

Four studies reported the outcome and all were classified as being of high-quality. The incidence of hypotension was equivalent between capnography and control arms in all studies except the one that lacked a definition for the endpoint. Between study heterogeneity was low ($I^2$ = 0%) and the estimated OR tended to one (OR 1.03, 95% CI 0.71–1.43; Supplement, Figure 7). There is no evidence of capnography monitoring influencing the incidence of this sedation-related adverse event.

## RESULTS: Supplemental oxygen

Although not a target endpoint in the protocol, six studies reported the requirement for oxygen supplementation. Of these, five studies were classified as high-quality and the primary analysis returned evidence of heterogeneity ($I^2$ = 41) and an OR of 0.83 (95% CI 0.59–1.17; Supplement, Figure 7). When analyzing all available data, the OR was 0.93 (95% CI 0.65–1.33).

**Figure 3** **The respiratory compromise cascade**

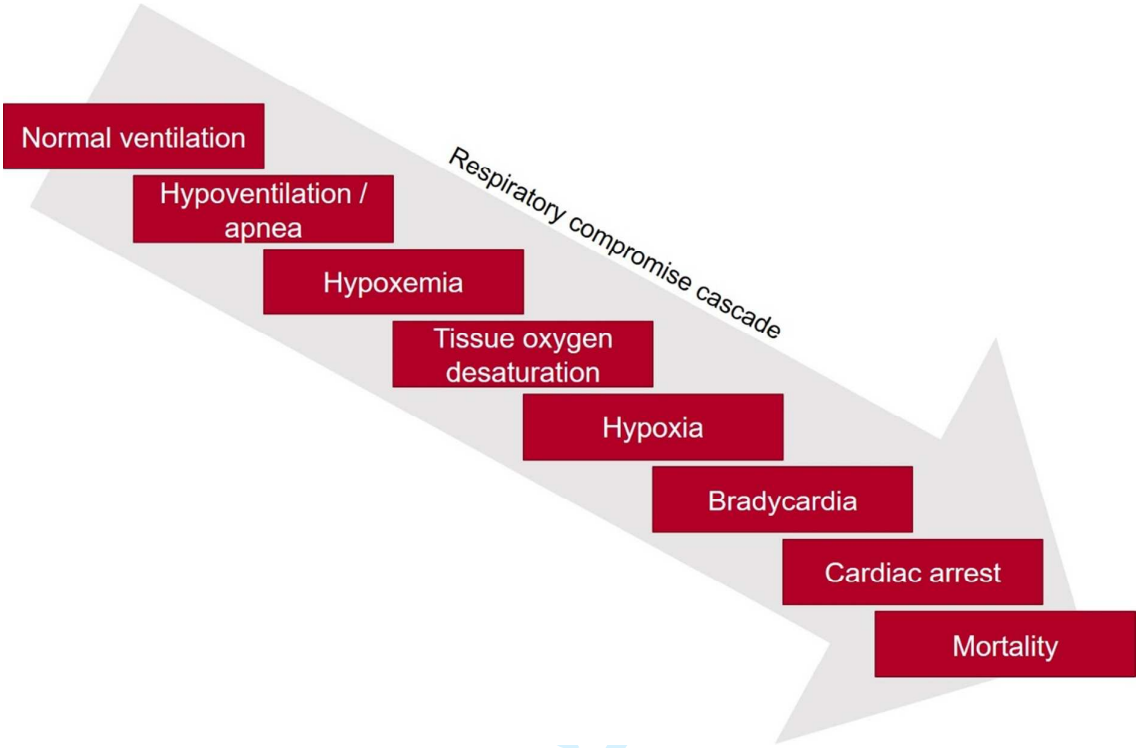


**Table 3** **The literature search strategy employed for PubMed was used as a basis for searching other literature databases**

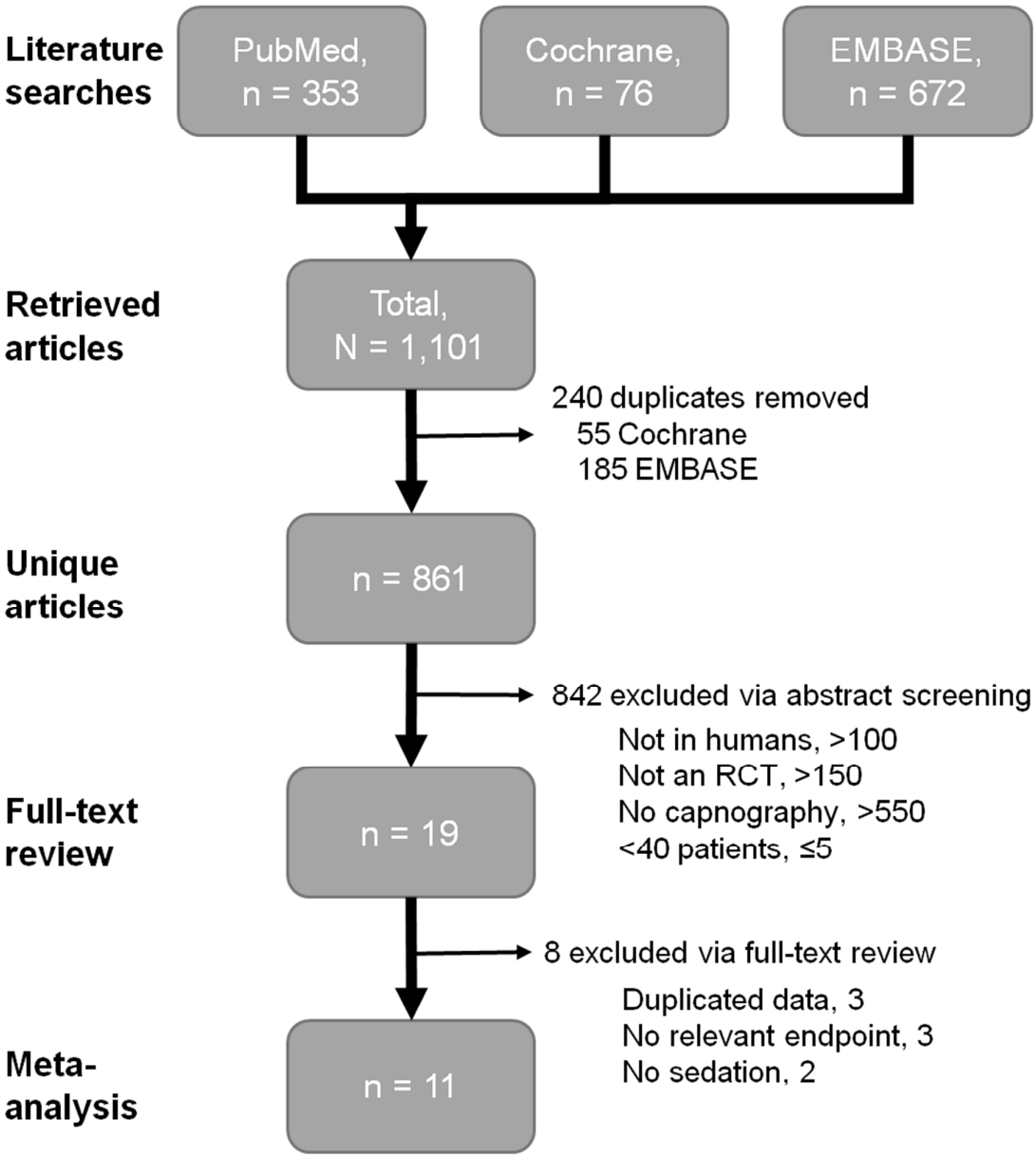
| Search | Search string | Results returned in PubMed |
|---|---|---|
| #1 | Capnogra*[tiab] OR ETCO2[tiab] OR (("end-tidal"[tiab] OR monitor*[tiab]) AND ("carbon dioxide"[tiab] or CO2[tiab])) OR sidestream[tiab] OR mainstream[tiab] OR microstream[tiab] OR "Capnography"[Mesh] OR (("Monitoring, Physiologic"[Mesh] OR "Monitoring, Intraoperative"[Mesh] OR "Intraoperative Care"[Mesh]) AND ("carbon dioxide"[tiab] or CO2[tiab])) | 20,192 |
| #2 | "Conscious Sedation"[Mesh] OR "Deep Sedation"[Mesh] OR "procedural sedation"[tiab] OR "moderate sedation"[tiab] or "conscious sedation"[tiab] or "deep sedation"[tiab] or sedati*[tiab] or anesthes*[tiab] | 175,021 |
| #3 | "Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial"[Publication Type] OR RCT[tiab] OR ((random*[tiab] OR clinic*[tiab]) AND control*[tiab] AND (trial[tiab] OR study[tiab])) | 770,467 |
| #4 | #1 AND #2 AND #3 | 410 |
| #5 | #4 AND "1995/01/01"[PDAT] : "2015/12/31"[PDAT] | 348 |

**Table 4** **Study exclusion and inclusion criteria**

| Exclusion criteria | Inclusion criteria |
|---|---|
| Research not in humans [106, 111] | Presents data for sedation (procedural, moderate, or deep) during ambulatory surgery |
| Not a randomized, controlled trial [172, 163] | Reports at least one of the following outcomes (apnea, aspiration, bradycardia, desaturation/hypoxia, hypotension, mortality) |
| Does not include capnography as the intervention [559, 566] | Uses time capnography (as opposed to volumetric) |
| Includes fewer than 40 patients in either arm [5, 2] | Is specific to the hospital setting |

Numbers in brackets provide the number of articles assigned that reason for exclusion by each of the two independent reviewers (RS, RFP)

**Figure 4** **Literature review flow diagram**



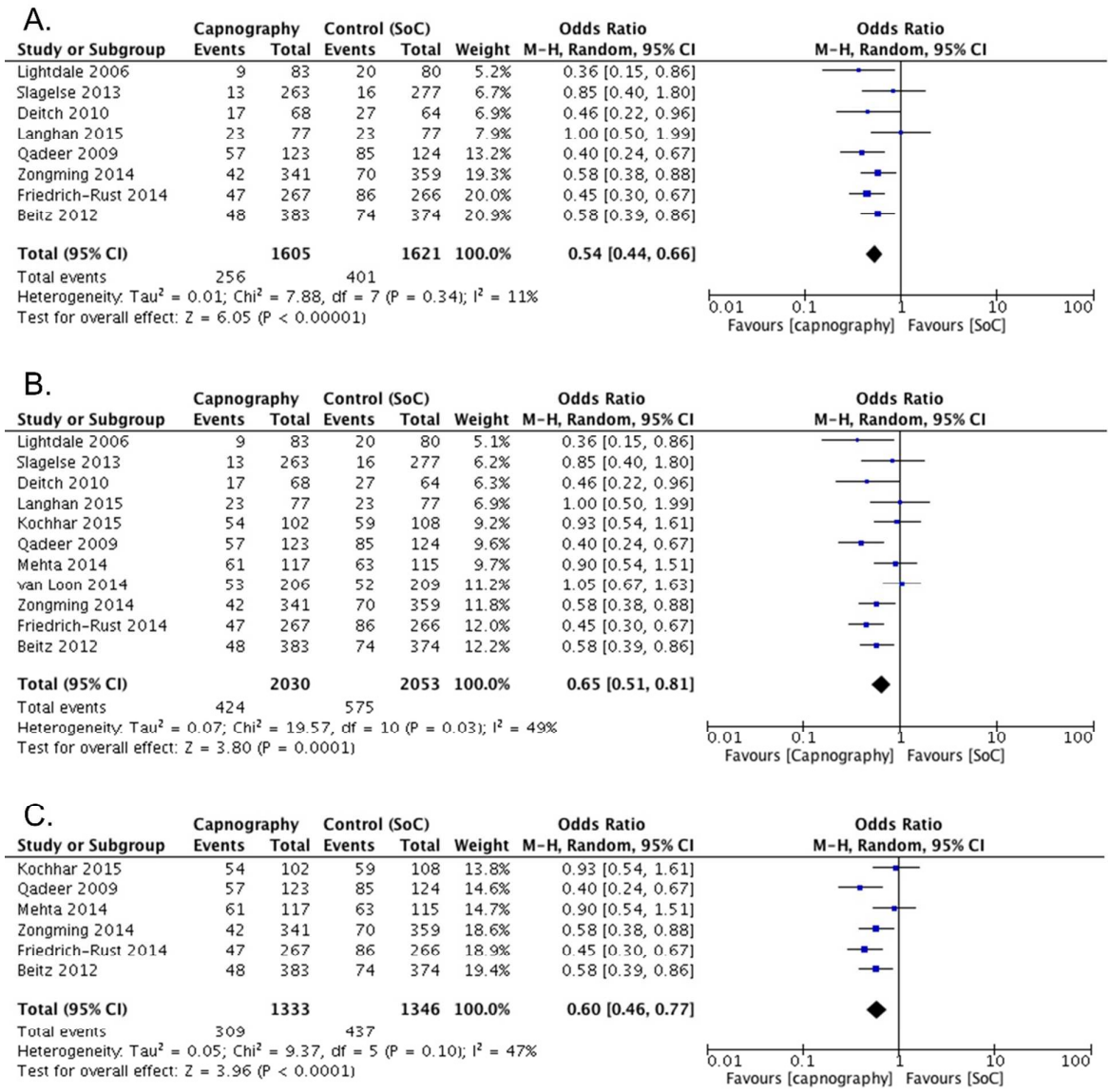

Full details of exclusion criteria provided by both independent reviewers during abstract screening are given in Table 2.

**Table 5 Endpoint definitions within included studies**

| Study | Desaturation, mild, $SpO_2$ % | Desaturation, severe, $SpO_2$ % | Apnea | Bradycardia, HR beats/minute | Hypotension, SBP mm Hg | Supplemental oxygen |
|---|---|---|---|---|---|---|
| Beitz 2012 | <90 | ≤85 | | <50 | <90 | >2 L/min |
| Deitch 2010 | <93 for ≥15 seconds | | | | | |
| Friedrich-Rust 2014 | <90 for ≥15 seconds | <85 | | <50 | <100 | >2 L/min |
| Kochhar 2015 | <90 for ≥10 seconds | ≤85 | No capnogram for ≥5 seconds | | | |
| Langhan 2015 | <95 | | | | | |
| Lightdale 2006 | <95 | | | | | |
| Mehta 2014 | <90 for ≥10 seconds | <85 | | | | |
| Qadeer 2009 | <90 for ≥15 seconds | ≤85 | No capnogram for ≥15 seconds | | Not defined | Any use |
| Slagelse 2013 | <92 | | | | | Any increase |
| van Loon 2014 | <91 | <81 | | | | Any increase |
| Zongming 2014 | <90 | ≤85 | | <50 | <90 | >3 L/min |

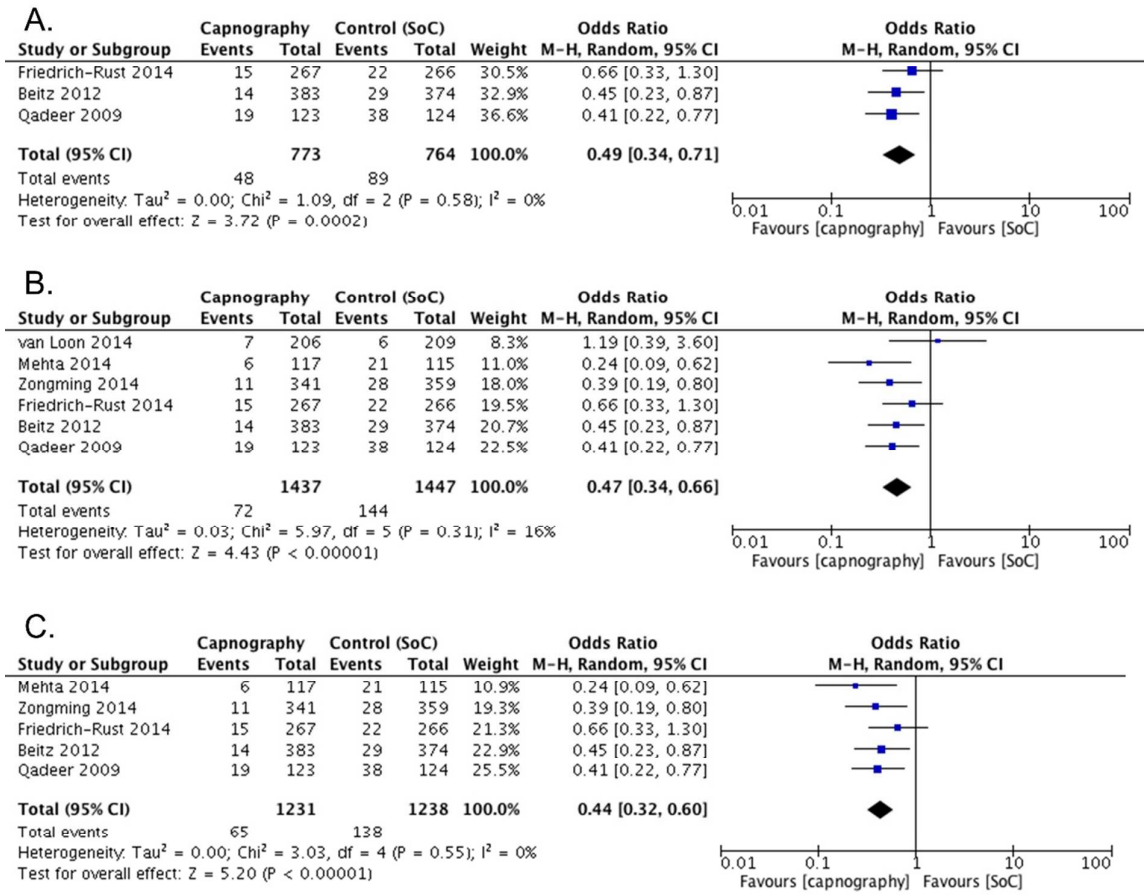
HR, Heart rate; SBP, Systolic blood pressure; $SpO_2$, Oxygen saturation

**Figure 5 Mild desaturation is reduced with capnography monitoring**



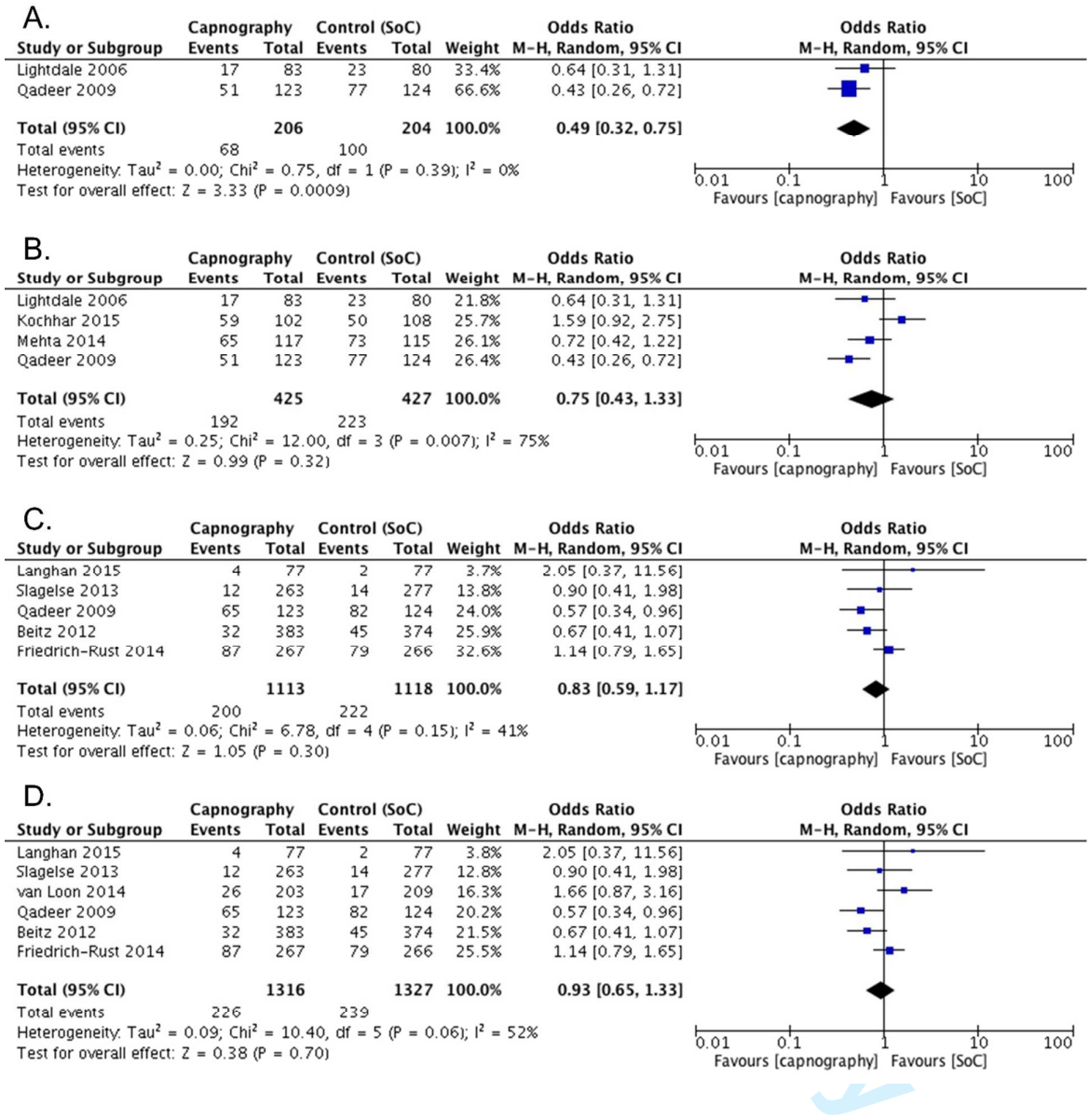

The odds ratios for the mild desaturation endpoint are presented for high-quality studies (primary analysis, A), all studies with data (B) and studies with an endpoint defined as oxygen saturation <90% (C). CI, Confidence interval; M-H, Mantel-Haenszel

**Figure 6** **Severe desaturation is reduced with capnography monitoring**



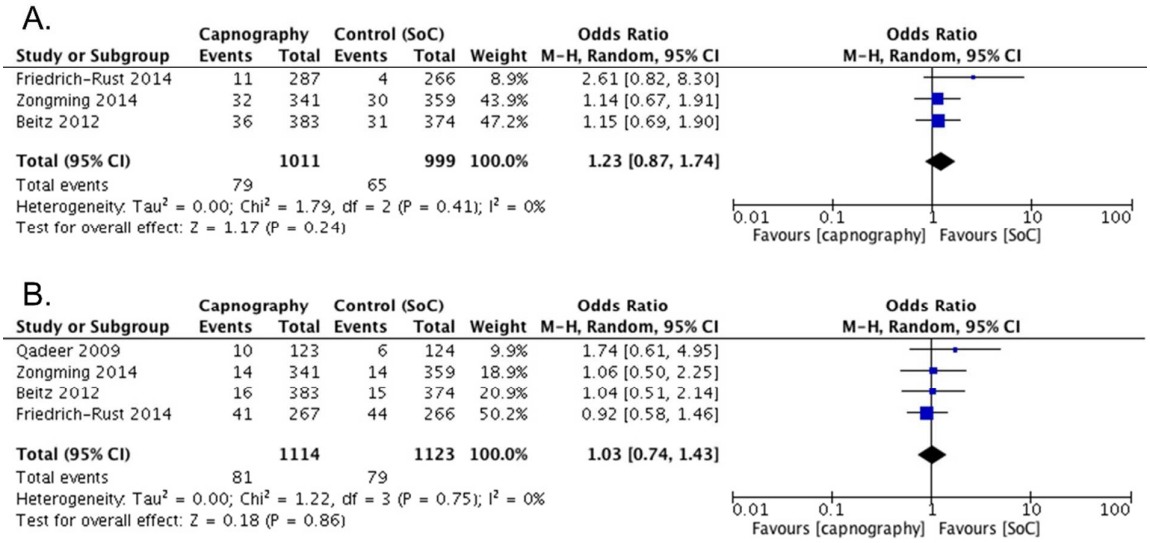

The odds ratios for the severe desaturation endpoint are presented for high quality studies (primary analysis, A), all studies with data (B) and studies with an endpoint defined as oxygen saturation <85% (C). CI, Confidence interval; M-H, Mantel-Haenszel

**Figure 7** **Evidence of reduced apnea incidence with capnography monitoring and a potential trend towards reduced need for supplemental oxygen**




The odds ratios for the apnea endpoint are presented for high quality studies (primary analysis, A) and all studies with data (B). Odds ratios for the use of supplemental oxygen are presented for high quality studies (primary analysis, C) and all studies with data (D). CI, Confidence interval; M-H, Mantel-Haenszel

**Figure 8** **Bradycardia tends to be increased with capnography monitoring, but there is little impact on the incidence of hypotension**




The odds ratios for the bradycardia (A) and hypotension (B) endpoints are presented for high quality studies (primary analysis), which were also all the studies with data. CI, Confidence interval; M-H, Mantel-Haenszel

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BMJ Open

# PATIENT SAFETY DURING PROCEDURAL SEDATION USING CAPNOGRAPHY MONITORING: A SYSTEMATIC REVIEW AND META-ANALYSIS



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| | |

# PATIENT SAFETY DURING PROCEDURAL SEDATION USING CAPNOGRAPHY MONITORING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

### Objective

To evaluate the effect of capnography monitoring on sedation-related adverse events during procedural sedation and analgesia (PSA) administered during ambulatory surgery relative to visual assessment and pulse oximetry alone.

### Design and Setting

Systematic literature review and random effects meta-analysis of randomized controlled trials (RCTs) reporting sedation-related adverse event incidence when adding capnography to visual assessment and pulse oximetry in patients undergoing PSA during ambulatory surgery in the hospital setting. Searches for eligible studies published between 1995 and 2015 (inclusive) were conducted in PubMed, the Cochrane Library and EMBASE without any language constraints. Searches were conducted in June, 2015, screening and data extraction was conducted by two independent reviewers, and study quality was assessed using a modified Jadad scale.

### Interventions

Capnography monitoring relative to visual assessment and pulse oximetry alone.

### Primary and Secondary Outcome Measures

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA.

### Results

The literature search identified 861 unique articles, of which 11 were ultimately included in the meta-analysis. Addition of capnography to visual assessment and pulse oximetry was associated with a significant reduction in the odds of apnea (OR 0.49, 95% CI 0.32–0.75), as well as mild (OR 0.54, 95% CI

0.44–0.66) and severe (OR 0.49, 95% CI 0.34–0.71) desaturation. Reduced occurrence of assisted ventilation was also observed with capnography, but this did not reach significance.

**Conclusions**

Meta-analysis of 11 RCTs published between 2006 and 2015 showed a reduction in respiratory compromise (from respiratory insufficiency to failure) during PSA with the inclusion of capnography monitoring. In particular, use of capnography was associated with less mild and severe oxygen desaturation, and may help to avoid the need for assisted ventilation.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

**Strengths**

- The studies included in the analysis were all published in 2006 or later, representing modern medical practice and providing consistent evidence of improvements in patient safety with the use of capnography monitoring.
- The study findings further substantiate a previously-published meta-analysis, which found that capnography monitoring was more likely to detect adverse events.

**Limitations**

- The level of sedation employed in each study was not uniformly reported, resulting in a mixture of different sedation levels in the primary analysis and precluding an analysis of outcomes by sedation level.
- As with all meta-analyses, the study findings may be affected by publication, search or selection bias affecting the studies ultimately included in the analysis; however, where possible, steps were taken to minimize the effects of bias on the analysis, but the degree to which these steps were successful is difficult to quantify.

## BACKGROUND AND AIMS

The administration of procedural sedation and analgesia (PSA) involves achieving a drug-induced depression in level of consciousness and pain to ensure the comfort and cooperation of patients undergoing non-surgical and minor surgical procedures. Significant adverse events associated with PSA are relatively rare but not inconsequential, and can include severe oxygen desaturation, bradycardia, hypotension, and cardiac arrest.[1,2] Consensus dictates that levels of sedation are directly related to patient risk during PSA, as is the potential for unintended progression from moderate to deep sedation.[3] Generally speaking, most cardiopulmonary events associated with PSA stem from poor or absent ventilation cascading into hypoxia, tissue injury and cardiac decompensation (Supplement, Figure 3). In turn, maintaining patient safety involves the identification of respiratory compromise to prompt the use of clinical intervention before further complications occur.[4,5,6,7,8,9]

In current clinical practice, patient monitoring during PSA often relies on visual assessment of ventilation and use of pulse oximetry, which reflects hypoxemia.[10,11,12,13,14] To date, a mandate to include capnography in patient monitoring, as a means of early detection of alveolar hypoventilation, has remained a topic of debate.[15] In particular, there has been a perceived gap between various study outcomes and evidence of improved patient safety. No studies have provided "hard proof" that addition of capnography to patient monitoring may reduce severe morbidity and mortality during PSA (in part because of ethical considerations to ensure patient rescue), and efforts to use meta-analysis to determine the utility of capnography to identify clinically significant respiratory depression have been faulted for large heterogeneity and non-standard endpoints.[16,17]

The primary aim of the present systematic review and meta-analysis was to understand whether capnography added to patient monitoring only (consisting of pulse oximetry and visual inspection of ventilation) reduces the incidence (or odds) of adverse events during PSA based on randomized controlled trials of patients undergoing a variety of surgical procedures. As a secondary aim, a power calculation was performed to determine the number of patients that would be required to

demonstrate a reduction in patient harm, defined as severe morbidity or mortality, in a prospective clinical trial of capnography versus visual assessment with pulse oximetry. The analysis was based on the hypothesis that earlier and more sensitive detection of ventilatory changes with capnography may allow for more timely intervention and prevention of potential adverse events, such as cardiac dysrhythmias. Throughout the analyses, we sought to provide the highest level of synthesized evidence with respect to the clinical utility of capnography monitoring during PSA. To mitigate potential pitfalls due to non-standard endpoints, particular emphasis was placed on maintaining a consistent definition of adverse events across all studies included.

## METHODS

Literature searches were conducted in PubMed, the Cochrane Library and EMBASE. Search terms were a combination of Medical Subject Heading (MeSH) terms and free-text searches within the articles title and abstract. Searches aimed to identify all literature reporting on randomized, controlled trials in patients receiving sedation during ambulatory surgery and in which visual assessment of ventilation and pulse oximetry monitoring (control) was compared with control plus capnography. No "grey" or unpublished literature was included in the search strategy and, as the review protocol was not registered in advance, the full search strategy (Supplement, Table 3) and additional details are provided in the Supplement. Only articles or abstracts published on or after January 1, 1995 were included and all searches were performed on June 17, 2015. No language exclusion was applied and inclusion was not dependent on the capnography monitor in use. After duplicate removal, title and abstract screening (Supplement, Table 4) was performed independently by RS and RFP. Full-text versions of all non-excluded articles were retrieved by MM and reviewed independently by RS and RFP. Data were then extracted independently by RS and RFP into data extraction forms in Microsoft Excel (Microsoft Corporation, Redmond, WA). Any discrepancies in the extracted data were resolved by reference to the original study, reaching consensus between RS and RFP. All extracted endpoint data were reviewed by JL and MMS for clinical utility to ensure that all synthesized data relate to

clinically equivalent endpoints. Extracted data included the number of patients with events and the population at risk, in addition to items required to assess article quality and bias. Reference lists of included studies were not searched.

**Endpoints**

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint, with severe desaturation defined as $SpO_2$ ≤85%), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA. The protocol was left open for the analysis of other patient safety endpoints that were reported by ≥3 studies. Cardiac arrest and death were considered to be representative of severe morbidity and mortality. Notably, the present analysis examined individual endpoints as opposed to composite endpoints (e.g. desaturation, apnea, or respiratory depression) and included analyses of more specific endpoints, such as oxygen desaturation <90% and <85%, were also conducted.

**Quality and potential bias**

Assessment of article quality was conducted on a study (as opposed to outcome) level using a modified Jadad score,[18] with additional criteria added to make the adaptation specific to monitoring. The Jadad score assesses studies based on their design (randomized and blinded) and their reporting (all patients accounted for), with a maximal score of 5 (high quality) and a low score of 0 (low quality). Additional data included here were endpoint definitions, patient population, hospital location at which patients underwent sedation, and the staff responsible for monitoring. In line with the Jadad score, items related to trial design could score up to twice as highly as items relating to trial reporting. The reporting of the inclusion/exclusion criteria and endpoint definitions scored one point each, and reporting the location of sedation, and the monitoring staff scored half-point point each, making the maximal score 8 (high quality). For the purposes of analyzing study quality, studies with scores of 0–5 were considered to be low quality, while studies scoring 5.5–8 were designated as high quality studies.

Risk of bias in results was evaluated independently from the quality assessment through the declaration of funding sources and conflicts of interest. If the study was funded by industry then the study scored 2, any conflicts of interest declared relating to industry funding outside of the current research publication scored 1. A study with low potential for bias, therefore, would have a score of 0. A high potential for bias was defined as a score of 3, while a score of 1–2 was considered to indicate moderate potential for bias. The absence of industry funding was not taken to signify an absence of bias, but the presence of industry funding or conflicts of interest was assumed to be an indicator of bias.[19]

**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.[20] Heterogeneity of data was evaluated using $Chi^2$ and $I^2$ statistics presented by Review Manager 5.3.4, with $I^2$ further categorized by the tentative Higgins *et al.* heterogeneity categories of: low, moderate and high.[21] The meta-analysis performed calculated the mean intervention effect across all eligible studies using (after analysis of heterogeneity) a random effects model as described by DerSimonian and Laird.[22] An estimate of between-study variation was provided by the Mantel-Haenszel methodology.[23] The outcome reported for each endpoint is the pooled mean odds ratio (OR) and its 95% confidence interval.

Sensitivity analyses were specified *a priori* and the tested conditions were: (1) inclusion of only moderate sedation, (2) inclusion of only studies with low risk of bias, (3) inclusion of only studies based in the US, (4) inclusion of only studies based in Europe, (5) exclusion of pediatric data, (6) exclusion of gender-specific studies, (7) exclusion of data in patients <30 years of age. No formal statistical comparisons were made between sensitivity analyses, and intervention effects were not calculated for the excluded studies, thereby mitigating the introduction of type 1 error into the analysis.

### Patient involvement

No patients, service users, carers or lay people were involved in the design or conduct of this study. Outcome measures were all related to patient safety during PSA, but were not developed based on an explicit elicitation of patient priorities, experience, and preferences.

## RESULTS

Literature searches of PubMed, the Cochrane Library and EMBASE returned 353, 76, and 672 articles, respectively. After removal of 240 duplicates (55 Cochrane, 185 EMBASE), 861 articles remained for abstract screening. Although reasons for exclusion varied (Supplement, Table 4), the two independent reviewers agreed upon a total of 19 articles to be retained for full-text review (Cohen's kappa, 1.0). Eight articles were excluded on full-text review (Supplement, Figure 4) because they: reported duplicate data (n=3), did not report patient safety data (n=3), and did not include sedation (n=2). The 11 articles included for analysis are presented in Table 1. All studies reported desaturation endpoints, although the definition did vary by study (Supplement, Table 5). Other endpoints were heterogeneously reported, but were in most cases reported by ≥3 studies making meta-analysis feasible as per the pre-defined protocol. Results reported are from random-effects models unless otherwise stated. Results for hypotension and use of supplemental oxygen are provided in the Supplement.

### Mild desaturation

All studies (Table 1) reported mild desaturation, with the definition varying from an oxygen saturation ($SpO_2$) of <95% to <90% for ≥15 seconds.[5,6,24,25,26,27,28,29,30,31,32] There was little evidence of heterogeneity ($I^2$ = 11%, low) in the primary analysis of high quality studies (n=8). Results indicated that capnography significantly reduced the odds of mild desaturation (OR = 0.54, 95% CI 0.44–0.66; Figure 1B); the odds of a mild desaturation event were approximately halved when capnography monitoring is used, compared with no use of capnography. If all available data were included (Supplement, Figure 5B), there was evidence of significant heterogeneity ($I^2$ = 49%, moderate) with an

OR of 0.65 (95% CI 0.51–0.81). Using exclusively studies with equivalent definitions of mild desaturation (<90%, n=6), evidence of heterogeneity ($I^2$ = 47%, moderate) was still present. The OR estimated from these studies was 0.60 (95% CI 0.46–0.77).

**Severe desaturation**

Six studies, of which three were classified as high quality, reported severe desaturation.[5,25,26,27,28,29] All but one of the studies defined severe desaturation as $SpO_2$ </≤85%. The primary analysis for this endpoint yielded an OR of 0.49 (95% CI 0.34–0.71), further supporting the significant reduction in the odds of desaturation with the inclusion of capnography (Figure 1). As with mild desaturation, there was no evidence of heterogeneity in the three high-quality studies ($I^2$ = 0%, low).

Synthesizing estimates from all available data supported the primary analysis (Supplement, Figure 6), the OR was reduced by 0.02 and the confidence interval tightened (OR 0.47, 95% CI 0.34–0.66). There was no significant heterogeneity between studies ($I^2$ = 16%, low). Focusing on the five studies reporting an endpoint of SpO2 </≤85%, there was no heterogeneity and the OR was estimated at 0.44 (95% CI 0.32–0.60). Overall, results support a greater than 50% reduction in the odds of severe desaturation events if capnography monitoring is used.

**Apnea**

Apnea was less widely reported or reported in combination with disordered respiration. Comparable endpoints were reported by four studies, of which two were high quality.[5,6,28,30] Primary analysis demonstrated a significant reduction in apnea with capnography monitoring (OR 0.49, 95% CI 0.32–0.75), with no evidence of heterogeneity (Supplement, Figure 7A). If all studies were included the degree of heterogeneity became significant ($I^2$ = 75%, high) and the outcome lacked significance at the 5% level (OR 0.75, 95% CI 0.43–1.33; Supplement Figure 7B). The difference between the primary and secondary analyses for apnea was driven by the Kochhar *et al.* study, which found apnea to be increased in the capnography arm.

**Bradycardia**

Three studies, all of high-quality, reported bradycardia outcomes.[26,27,29] Its definition (heart rate <50 beats/minute) was consistent among trials and there was no evidence of between study heterogeneity ($I^2$ = 0%, low). In all studies, the incidence of bradycardia was higher in the capnography arm compared with the control arm (Supplement, Figure 8). Overall, capnography monitoring was associated with a non-significant increase in bradycardia (OR 1.23, 95% CI 0.87–1.74).

**Assisted ventilation**

Only one study reported one instance of what was termed "respiratory failure," that was treated with assisted bag-mask ventilation.[26] In contrast, the number of studies reporting assisted and/or bag-mask ventilation was sufficient to perform a meta-analysis of this endpoint as a surrogate for respiratory failure. In total, five studies reported this and all were classified as high-quality.[5,26,27,31,32] The primary analysis showed no evidence of heterogeneity and an OR of 0.83 (95% CI 0.59–1.17; Supplement Figure 7C). In every case, the need to provide assisted ventilation was lower in the capnography arm compared with the control arm (Figure 2). The lack of significance reflects the low number of observed events and the resulting lack of power. For this reason, a Peto fixed-effects model was used to estimate the Peto OR, which was 0.54 (95% CI, 0.26–1.12).

**Sensitivity analyses**

A series of sensitivity analyses were conducted in which the studies included in the estimation of the OR were varied. The results of these analyses are presented in Table 2 and show that results were generally robust to the studies included for data synthesis. There were limited data available to assess the impact of capnography monitoring during moderate sedation. Data available indicate that the impact of capnography is reduced relative to deep sedation. With respect to severe desaturation events, there was also a substantial difference between US and European data. In Europe, addition of capnography monitoring was estimated to reduce the odds of severe desaturation by about 40%; for the US based studies this increased to 65%.

## DISCUSSION

The findings of a meta-analysis of recent RCTs comparing visual assessment of ventilation and pulse oximetry monitoring with and without capnography during PSA showed that the odds of apnea and oxygen desaturation events were significantly reduced with the use of capnography. Other endpoints that could be affected by capnography monitoring were also considered and the majority was found to be associated with substantial, but not significant, benefits to patient safety. Specifically, and of potential clinical importance, was the consistency of data across multiple high-quality clinical trials reporting a reduced incidence of assisted ventilation with capnography monitoring. No endpoints assessed in the meta-analysis indicated significant patient safety concerns with capnography.

Physician concerns for patient safety often focus on mortality and severe morbidity. There was no evidence that these outcomes differed between control and capnography arms in the present meta-analysis. The incidence of these events during nurse-administered PSA has been reported to be 1 event per 303 procedures (0.33%).[33] Taking this value and using the assumption that capnography could prevent 50% of events, the formula provided by Zhong (2009) to calculate the trial size required to demonstrate statistical superiority returned 27,726 patients.[34] Switching to an assumption that capnography would prevent 10% of events, the required trial size was calculated to be >900,000 patients. Not only is the feasibility of performing such a superiority trial low, but meta-analyses such as the present study, are not able to detect this difference from the relatively small number of existing lower-powered studies currently available in peer-reviewed medical literature.

The analysis is timely given the ongoing lively debate as to whether the addition of capnography to patient monitoring during PSA adds value.[17] Without doubt, potential technical and financial burdens have further limited adoption of capnography monitoring in various clinical settings.[15,17] Nevertheless, it is important to recognize that patient safety benefits may offset a number of these concerns if the outcomes are applicable to current medical practice.[35] In this regard, the 11 trials identified in the present analysis were all relatively recent, with the first published study identified in 2006. The data

used in the meta-analysis therefore represents modern medical practice, and provides consistent evidence of improvements in patient safety with the use of capnography monitoring.

These findings further substantiate a previously published meta-analysis (Waugh *et al.*), which found that capnography monitoring was more likely to detect adverse events, but was faulted for large endpoint heterogeneity.[16] In the present meta-analysis, we focused on identifying high-quality studies, and on maintaining consistent definitions across all included studies, thereby minimizing potential for heterogeneity. The results show that the addition of capnography to patient monitoring during PSA results in increased patient safety, with significant reductions in apnea, as well as mild and severe levels of oxygen desaturation.

More recently, a meta-analysis by Conway *et al.* reported a significant benefit with capnography during colonoscopy only with respect to hypoxemia. However, the study identified and screened only a fraction of the literature included in the present analysis (388 papers in Conway *et al.*, compared with 861 papers in the current study) and retrieved fewer randomized controlled trials (6 versus 11). In addition, Conway *et al.* excluded two trials in which an independent observer monitored capnography output for all patients, and signaled to the attending physician when respiratory compromise was identified with capnography either immediately (intervention) or after a specified delay (control).[5,6] The rationale for this was to prevent unnecessary patient harm while avoiding investigator bias. Based on our understanding, the two trials excluded in the Conway *et al.* analysis are the only studies in the literature that could be considered fully blinded. Among the other studies, the attending physician would have been aware of study arm assignment.[25,27,32]

As with other major assessment tools such as Delphi, Consort, and the Cochrane risk of bias tool, blinding is an integral part of the Jadad score used in the present analysis.[18,36] The trials excluded from the Conway *et al.* analysis are both considered to be "high quality" in the present analysis, driven in part by the inclusion of blinding in the scoring methodology. Other included trials, though potentially more representative of current clinical practice, are open to operator bias, the consequences of which were demonstrated in 2012 by Veerus *et al.*[37]

One potential limitation of the present quality appraisal approach was the lack of validation of the modifications to the Jadad score; however, as may be expected, the modified score does significantly correlate with the raw Jadad score (adjusted $R^2 = 0.83$, $p < 0.01$). Furthermore, analysis of mild desaturation data using a mixed model that took the modified Jadad score as a covariate, found that the modified Jadad score accounted for 97.5% of the heterogeneity and had both an intercept ($p < 0.05$) and gradient ($p < 0.01$) significantly different from zero. When blinding was removed from the score, the model accounted for only 49.9% of heterogeneity and did not reach significance. Although there is a clear distinction between real-world practice and a clinical trial, these *post-hoc* analyses demonstrate the potential importance of blinding in trial design. Given the exclusion of blinded trials, the results of the Conway analysis should be interpreted with this in mind. Nevertheless, the finding of consistent outcomes for hypoxemia in Conway *et al.* (relative risk 0.59, 95% CI 0.48 to 0.73) and mild desaturation in the present analysis (OR 0.54, 95% CI 0.44 to 0.66; RR 0.65, 95% CI 0.57 to 0.74) was encouraging. These findings are also aligned with a European randomized, controlled trial of capnography that was published after the analysis was complete.[38]

Another ongoing debate in PSA concerns the clinical importance of seemingly minor endpoints, such as mild desaturation (oxygenation <90% for 15 seconds). Although such endpoints have traditionally been considered transient and perhaps clinically insignificant during PSA, several recent studies of common intraoperative events have suggested that mild desaturation may have more impact on post-surgical outcomes than has previously been recognized.[39] For example, Dunham *et al.* looked retrospectively and determined that surgical patients who experienced perioperative hypoxemia/desaturation had a significant increase in their length of hospital stay (+2.0 days, $p<0.0001$).[40] In turn, the impact of transient desaturation during PSA in terms of patient outcomes and quality of life may yet be of importance but remains to be determined.

Over all of the studies included in the analysis, there were no reports of patient mortality. Only the largest trials reported any requirement for assisted/bag-mask ventilation, which is used as an intervention and thereby a proxy measure for potentially life-threatening events. Although it is

generally accepted that much larger studies would be useful to assess whether or not capnography monitoring impacts patient major morbidity and mortality, there has been no determination of the trial size that would be required. Power calculations suggest such a large randomized controlled trial is likely to be impractical.

For healthcare providers, the most significant finding may be the consistency of data surrounding apnea and severe oxygen desaturation, as well as reduced need for assisted ventilation with capnography. Two closed claim reviews both found that inadequate oxygenation/ventilation was the most frequent event leading to a claim related to PSA outside the operating room.[41,42] The potential cost burden is demonstrated by the median cost of a claim settled being USD 330,000 (in 2007 USD).[41] The authors reported that better monitoring would have reduced the number of claims.[41] A similar message was returned following the fourth National Audit Project in the UK, which analyzed major complications of airway management in the National Health Service and determined that capnography monitoring could have led to earlier identification of airway obstruction, potentially preventing 74% of death or neurological injury cases.[43,44] Studies included in the present meta-analysis reported that disordered ventilation as detected by capnography preceded desaturation events by 30 to 60 seconds.

The meta-analysis did find an increase in bradycardia with capnography monitoring that was non-significant, but consistent among the three included studies reporting the endpoint. However, in each of the three trials, patients in the capnography arm had larger doses and increased use of multiple agents for inducing PSA. Such confounding is plausible, and may not be unusual. In a non-blinded study published after the present analysis, the authors identified increased incidence of hypotension in the capnography arm, in addition to higher sedative doses, patient ASA class, and incidence of comorbidities.[45] All other findings of the current analysis were in line with expectations around the potential benefits of capnography. Earlier identification of respiratory compromise appears to result in more timely intervention and prevention of its escalation into patient harm.

As with all data synthesis projects, the present study is only as accurate and reliable as the data underlying it. In the literature, there are examples of newly-published clinical trials that do not align with the results of published meta-analyses, and meta-analysis results changing on the publication of new data.[46,47] The systematic nature of study identification and inclusion criteria in the present analysis was designed to identify all available literature and provide the most robust estimates of intervention effect. However, the included studies came from a variety of hospital settings, in which the rate of patient safety events might vary. Analyses for particular settings were undertaken, but were then limited by reduced data availability. In total, this analysis represented 4,083 patients (control 2,053 and Capnography 2,030) over 11 studies. Between trials, the number of patients enrolled varied between 132 and 757. Notably, only the four studies including >500 patients identified rare outcomes, such as differences in use of assisted ventilation.

## CONCLUSIONS

The results of this comprehensive meta-analysis of high-quality clinical trials provide clear and consistent evidence of decreased respiratory compromise when capnography monitoring is used during procedural sedation and analgesia (PSA). Specifically, the analysis identified a statistically significant and clinically meaningful reduction in apnea, as well as in mild and severe oxygen desaturation. Large, well designed, randomized controlled trials to provide direct links between use of capnography and reduction in patient harm may not be feasible. In turn, calls for this type of primary evidence may delay adoption of capnography monitoring during PSA as a valuable tool for early intervention and improved patient safety.

**Word Count** 5,140

## AUTHOR CONTRIBUTIONS

MM formulated the research question; RFP and RS devised the search strategy and data extraction protocol, which was critically reviewed and revised by MM, JRL and MMRFS; RFP and RS then conducted the literature searches, screening, data extraction, and meta-analysis, and co-wrote the manuscript; MM, JRL and MMRFS critically reviewed the manuscript and made substantive revisions prior to submission.

## DATA SHARING STATEMENT

All data used to derive the outcomes presented in the study are documented in the manuscript and supplementary materials. No additional data are therefore available.

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## TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## ETHICAL APPROVAL

No ethical approval was required for the study as all data were derived from published data; neither animal nor human subjects were enrolled as part of the present study.

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## FINANCIAL AND COMPETING INTEREST DISCLOSURE

All authors have completed the Unified Competing Interest forms at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

- Michael Mestek is a full-time employee of Medtronic plc.
- Richard Pollock is a full-time employee of Ossian Health Economics and Communications GmbH, which received research and consultancy fees from Medtronic plc. to conduct the literature review and meta-analysis and prepare the manuscript.
- Rhodri Saunders was a full-time employee of Ossian Health Economics and Communications GmbH at the time of performing the meta-analysis and is currently a director of Coreva Scientific GmbH & Co. KG.
- Michel MRF Struys's research group/department received grants and funding from The Medicines Company (USA), Masimo (USA), Fresenius (Germany), Acacia Design (The Netherlands), Medtronic (USA) and honoraria from The Medicines Company (USA), Masimo (USA), Fresenius (Germany), Baxter (USA), Medtronic (USA), Demed Medical (Belgium).
- Jenifer R. Lightdale has served as a consultant for Medtronic and Norgine, and has received speaker honorarium from Mead-Johnson and Perrigo.

## TABLES AND FIGURES

**Table 1** **Included studies reporting endpoints of interest**

| Study (reference) | Country | Trial dates | Modified Jadad | Potential for bias | Hospital setting | Depth of sedation | Sedative | Monitoring staff | Oxygen at baseline | N (control, Cap) |
|---|---|---|---|---|---|---|---|---|---|---|
| Beitz 2012[26] | Germany | Feb-10, Jan-11 | 5.5 | High: 3 | Colonoscopy | "adequate" | Propofol | Not specified | 2 L/minute | 757 (374, 383) |
| Deitch 2010[24] | US | Nov-06, Feb-08 | 5.5 | Low: 0 | Emergency department | Moderate | Propofol | Not specified | 3 L/minute | 132 (64, 68) |
| Friedrich-Rust 2014[27] | Germany | Jun-12, May-13 | 6 | Low: 0 | Colonoscopy | Deep | Propofol+ | Anesthesiologist or sedation-trained nurse | 2 L/minute | 533 (266, 267) |
| Kochhar 2015[30] | US | NA | 3.5 | Low: 0 | EGD | Moderate | Opioid and BZP | Not specified | Not specified | 210 (108, 102) |
| Langhan 2015[31] | US | Sep-11, Jan-13 | 6 | Low: 0 | Pediatric emergency department | NA | Ketamine, midazolam | "Treating staff" | None | 154 (77, 77) |
| Lightdale 2006[6] | US | Dec-03, Nov-04 | 8 | Low: 0 | Endoscopy | Moderate | Fentanyl, midazolam | Independent observer | 2 L/minute | 163 (80, 83) |
| Mehta 2014[28] | US | NA | 3.5 | Low: 0 | Colonoscopy | Moderate | Opioid and BZP | Not specified | Not specified | 232 (115, 117) |
| Qadeer 2009[5] | US | Jan-07, May-08 | 7.5 | Moderate: 1 | ERCP and EUS | NA | Midazolam+ | Independent observer | None | 247 (124, 123) |
| Slagelse 2013[32] | Denmark | Sep-10, Jan-11 | 6 | Low: 0 | Endoscopy | NA | Propofol | Sedation-trained nurse | 2-3 L/minute | 540 (277, 263) |
| van Loon 2014[25] | Netherlands | Apr-10, Jan-11 | 5 | Low: 0 | Gynecology | Deep | Propofol | Medical team providing sedation | None | 415 (209, 206) |
| Zongming 2014[28] | China | Nov-10, May-13 | 6 | Low: 0 | Abortion | Deep | Propofol | Anesthesiologist | 3 L/minute | 700 (359, 341) |

+, in combination with multiple other agents; BZP, benzodiazepine; Cap, Capnography (arm); EGD, Esophagogastroduodenoscopy; ERCP, Endoscopic retrograde cholangiopancreatography; EUS, Endoscopic ultrasonography

**Figure 1 Severe and mild desaturation are reduced with capnography monitoring**

The odds ratios for the mild desaturation endpoint are presented for high-quality studies (primary analysis) for severe desaturation (A) and mild desaturation (B). CI, Confidence interval; M-H, Mantel-Haenszel

**Figure 2 The need for assisted ventilation is consistently reduced with capnography monitoring**

The odds ratios for the assisted ventilation endpoint are presented for high quality studies, which coincided with all studies that reported data for the endpoint. CI, Confidence interval; M-H, Mantel-Haenszel

**Table 2** **Sensitivity analyses around the primary analyses, treatment effect is the odds ratio [95% confidence interval]**

| Scenario | Desaturation, mild | Desaturation, severe | Apnea | Bradycardia | Hypotension | Assisted ventilation | Supplemental oxygen |
|---|---|---|---|---|---|---|---|
| **Base case (high quality studies)** | **0.54 [0.44, 0.66]** RR: 0.65 [0.57, 0.74] | **0.49 [0.34, 0.71]** RR: 0.54 [0.39, 0.75] | **0.49 [0.32, 0.75]** RR: 0.68 [0.54, 0.85] | **1.23 [0.87, 1.74]** RR: 1.20 [0.88, 1.65] | **1.03 [0.74, 1.43]** RR: 1.02 [0.76, 1.37] | **0.54 [0.25, 1.16]** RR: 0.55 [0.26, 1.16] | **0.85 [0.65, 1.11]** RR: 0.89 [0.76, 1.05] |
| All studies with data | 0.65 [0.51, 0.81] | 0.47 [0.34, 0.66] | 0.75 [0.43, 1.33] | 1.23 [0.87, 1.74] | 1.03 [0.74, 1.43] | 0.54 [0.25, 1.16] | 0.93 [0.65, 1.33] |
| Moderate sedation | 0.67 [0.44, 1.04] | – | 0.92 [0.52, 1.64] | – | – | – | – |
| US only | 0.64 [0.44, 0.93] | 0.35 [0.21, 0.59] | 0.75 [0.43, 1.33] | – | – | – | 0.82 [0.27, 2.54] |
| Europe only | 0.65 [0.52, 0.81] | 0.61 [0.40, 0.93] | – | 1.46 [0.70, 3.03] | 0.95 [0.64, 1.40] | 0.57 [0.25, 1.29] | 0.91 [0.63, 1.30] |
| Studies with potential bias excluded | 0.69 [0.58, 0.82] | 0.51 [0.28, 0.90] | 0.92 [0.52, 1.64] | 1.46 [0.69, 3.08] | 0.95 [0.64, 1.41] | 0.56 [0.25, 1.23] | 1.12 [0.81, 1.55] |
| Studies in pediatrics excluded | 0.64 [0.54, 0.75] | 0.47 [0.34, 0.66] | 0.79 [0.38, 1.65] | 1.23 [0.87, 1.74] | 1.03 [0.74, 1.43] | 0.54 [0.25, 1.16] | 0.90 [0.63, 1.31] |
| Gender-specific studies excluded | 0.60 [0.50, 0.72] | 0.45 [0.31, 0.63] | 0.75 [0.43, 1.33] | 1.23 [0.87, 1.74] | 1.02 [0.71, 1.48] | 0.57 [0.25, 1.29] | 0.83 [0.59, 1.17] |
| Studies with mean age >30 years | 0.59 [0.49, 0.70] | 0.49 [0.33, 0.74] | 0.79 [0.38, 1.65] | 1.23 [0.87, 1.74] | 1.03 [0.74, 1.43] | 0.54 [0.25, 1.16] | 0.80 [0.57, 1.14] |

CI, confidence interval; OR, odds ratio; RR, risk ratio; US, United States

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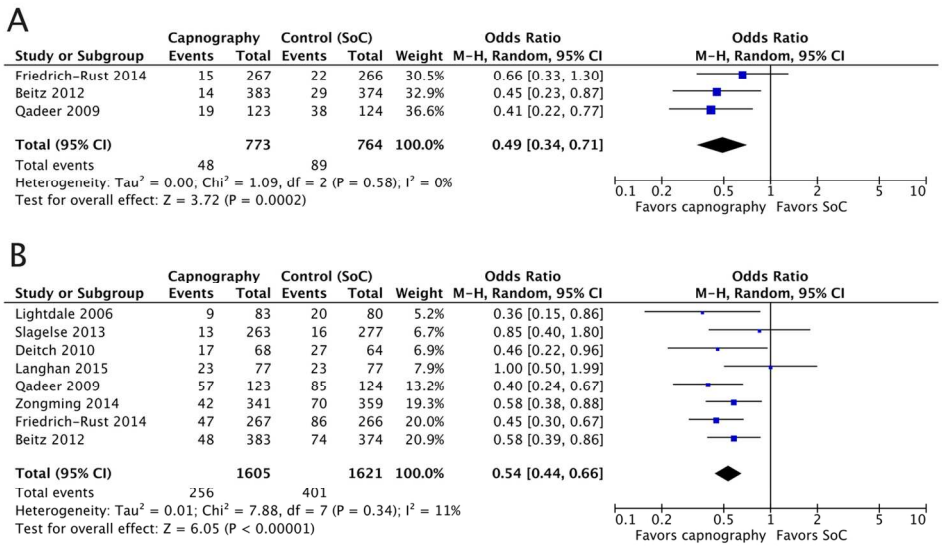
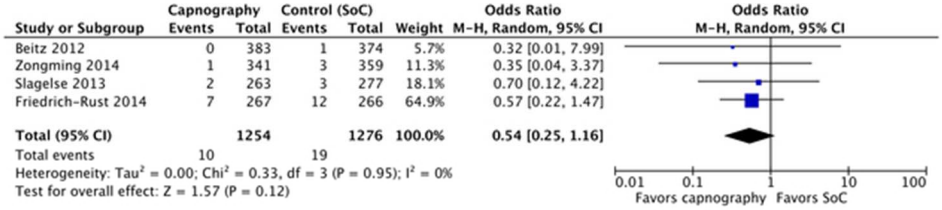



Severe and mild desaturation are reduced with capnography monitoring
Figure 1
128x78mm (300 x 300 DPI)




The need for assisted ventilation is consistently reduced with capnography monitoring
Figure 2
56x15mm (300 x 300 DPI)

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 22 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 22 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 23 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 19,24 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 16 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 17,24-27 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 17,24-27 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 18 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 18 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12-13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 14 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

# PATIENT SAFETY DURING PROCEDURAL SEDATION USING CAPNOGRAPHY MONITORING: A SYSTEMATIC REVIEW AND META-ANALYSIS



| | |
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# PATIENT SAFETY DURING PROCEDURAL SEDATION USING CAPNOGRAPHY MONITORING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

### Objective

To evaluate the effect of capnography monitoring on sedation-related adverse events during procedural sedation and analgesia (PSA) administered during ambulatory surgery relative to visual assessment and pulse oximetry alone.

### Design and Setting

Systematic literature review and random effects meta-analysis of randomized controlled trials (RCTs) reporting sedation-related adverse event incidence when adding capnography to visual assessment and pulse oximetry in patients undergoing PSA during ambulatory surgery in the hospital setting. Searches for eligible studies published between January 1, 1995 and December 31, 2016 (inclusive) were conducted in PubMed, the Cochrane Library and EMBASE without any language constraints. Searches were conducted in January 2017, screening and data extraction were conducted by two independent reviewers, and study quality was assessed using a modified Jadad scale.

### Interventions

Capnography monitoring relative to visual assessment and pulse oximetry alone.

### Primary and Secondary Outcome Measures

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA.

### Results

The literature search identified 1,006 unique articles, of which 13 were ultimately included in the meta-analysis. Addition of capnography to visual assessment and pulse oximetry was associated with a significant reduction in mild (RR 0.77, 95% CI 0.67–0.89) and severe (RR 0.59, 95% CI 0.43–0.81)

desaturation, as well as in the use of assisted ventilation (RR 0.47, 95% CI 0.23–0.95). No significant difference in other endpoints were identified.

**Conclusions**

Meta-analysis of 13 RCTs published between 2006 and 2016 showed a reduction in respiratory compromise (from respiratory insufficiency to failure) during PSA with the inclusion of capnography monitoring. In particular, use of capnography was associated with less mild and severe oxygen desaturation, which may have helped to avoid the need for assisted ventilation.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

**Strengths**

- The studies included in the analysis were all published in 2006 or later, representing modern medical practice and providing clinically relevant evidence of improvements in patient safety with the use of capnography monitoring.
- The study findings further substantiate a previously-published meta-analysis, which found that capnography monitoring was more likely to detect adverse events. It also suggests that superior detection may reduce the use of clinical interventions intended to rescue patients from potential adverse outcomes.

**Limitations**

- The level of sedation employed in each study was not uniformly reported, resulting in a mixture of different sedation levels in the primary analysis and precluding an analysis of outcomes by sedation level.
- As with all meta-analyses, the study findings may be affected by publication, search or selection bias affecting the studies ultimately included in the analysis; however, where possible, steps were taken to minimize the effects of bias on the analysis, but the degree to which these steps were successful is difficult to quantify.

## BACKGROUND AND AIMS

The administration of procedural sedation and analgesia (PSA) involves achieving a drug-induced depression in level of consciousness and pain to ensure the comfort and cooperation of patients undergoing non-surgical and minor surgical procedures. Significant adverse events associated with PSA are relatively rare but not inconsequential, and can include severe oxygen desaturation, bradycardia, hypotension, and cardiac arrest.[1,2] Consensus dictates that levels of sedation are directly related to patient risk during PSA, as is the potential for unintended progression from moderate to deep sedation.[3] Generally speaking, most cardiopulmonary events associated with PSA stem from poor or absent ventilation cascading into hypoxia, tissue injury and cardiac decompensation (Supplementary Figure 1). In turn, maintaining patient safety involves the identification of respiratory compromise to prompt the use of clinical intervention before further complications occur.[4,5,6,7,8,9]

In current clinical practice, patient monitoring during PSA often relies on visual assessment of ventilation and use of pulse oximetry, which reflects hypoxemia.[10,11,12,13,14] To date, a mandate to include capnography in patient monitoring, as a means of early detection of alveolar hypoventilation, has remained a topic of debate.[15] In particular, there has been a perceived gap between various study outcomes and evidence of improved patient safety. No studies have provided "hard proof" that addition of capnography to patient monitoring may reduce severe morbidity and mortality during PSA (in part because of ethical considerations to ensure patient rescue). Previous efforts to use meta-analysis to determine the utility of capnography to identify clinically significant respiratory depression have been faulted for large heterogeneity and non-standard endpoints.[16,17]

The primary aim of the present systematic review and meta-analysis was to understand whether capnography added to patient monitoring only (consisting of pulse oximetry and visual inspection of ventilation) reduces the incidence (or odds) of adverse events during PSA based on randomized controlled trials of patients undergoing a variety of surgical procedures. As a secondary aim, a power calculation was performed to determine the number of patients that would be required to

demonstrate a reduction in patient harm, defined as severe morbidity or mortality, in a prospective clinical trial of capnography versus visual assessment with pulse oximetry. The analysis was based on the hypothesis that earlier and more sensitive detection of ventilatory changes with capnography may allow for more timely intervention and prevention of potential adverse events, such as cardiac dysrhythmias. Throughout the analyses, we sought to provide the highest level of synthesized evidence with respect to the clinical utility of capnography monitoring during PSA. To mitigate potential pitfalls due to non-standard endpoints, particular emphasis was placed on maintaining a consistent definition of adverse events across all studies included.

## METHODS

Literature searches were conducted in PubMed, the Cochrane Library and EMBASE. Search terms were a combination of Medical Subject Heading (MeSH) terms and free-text searches within the articles title and abstract. Searches aimed to identify all literature reporting on randomized, controlled trials in patients receiving sedation during ambulatory surgery and in which visual assessment of ventilation and pulse oximetry monitoring (control) was compared with control plus capnography. "Grey" or unpublished literature (including congress abstracts) was included in the search strategy and, as the review protocol was not registered in advance, the full search strategy (Supplementary Table 1) and additional details are provided in the Supplement. Only articles or abstracts published on or after January 1, 1995 were included and all searches were performed on January 15, 2017. A previous systematic review in this area did not identify any study prior to 1995,[16] and studies published prior to 1995 were considered unlikely to reflect modern clinical practice. No language exclusion was applied and inclusion was not dependent on the capnography monitor in use. After duplicate removal, title and abstract screening (Supplementary Table 2) was performed independently by RS and RFP using Sourcerer (Covalence Research Ltd, London UK).[18] Full-text versions of all non-excluded articles were retrieved by MM and reviewed independently by RS and RFP. Data were then extracted independently by RS and RFP into data extraction forms in Microsoft Excel (Microsoft Corporation, Redmond, WA).

Any discrepancies in the extracted data were resolved by reference to the original study, reaching consensus between RS and RFP. All extracted endpoint data were reviewed by JL and MMS for clinical utility to ensure that all synthesized data relate to clinically equivalent endpoints. Extracted data included the number of patients with events and the population at risk, in addition to items required to assess article quality and bias. Reference lists of included studies were not searched.

**Endpoints**

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint, with severe desaturation defined as $SpO_2$ ≤85%), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA. The protocol was left open for the analysis of other patient safety endpoints that were reported by ≥3 studies. Cardiac arrest and death were considered to be representative of severe morbidity and mortality. Notably, the present analysis examined individual endpoints as opposed to composite endpoints (e.g. desaturation, apnea, or respiratory depression) and included analyses of more specific endpoints, such as oxygen desaturation <90% and <85%.

**Quality and potential bias**

Assessment of article quality was conducted on a study (as opposed to outcome) level using a modified Jadad score,[19] with additional criteria added to make the adaptation specific to monitoring. The Jadad score assesses studies based on their design (randomized and blinded) and their reporting (all patients accounted for), with a maximal score of 5 (high quality) and a low score of 0 (low quality). Additional data included here were endpoint definitions, patient population, hospital location at which patients underwent sedation, and the staff responsible for monitoring. In line with the Jadad score, items related to trial design could score up to twice as highly as items relating to trial reporting. The reporting of the inclusion/exclusion criteria and endpoint definitions scored one point each, and reporting the location of sedation, and the monitoring staff scored half-point point each, making the maximal score 8 (high quality). For the purposes of analyzing study quality, studies with scores of 0–

5.5 were considered to be low quality, while studies scoring 6.0–8.0 were designated as high-quality studies.

Risk of bias in results was evaluated independently from the quality assessment through the declaration of funding sources and conflicts of interest. If the study was funded by industry then the study scored 2, any conflicts of interest declared relating to industry funding outside of the current research publication scored 1. A study with low potential for bias, therefore, would have a score of 0. A high potential for bias was defined as a score of 3, while a score of 1–2 was considered to indicate moderate potential for bias. The absence of industry funding was not taken to signify an absence of bias, but the presence of industry funding or conflicts of interest was assumed to be an indicator of bias.[20]

**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.[21] Heterogeneity of data was evaluated using $Chi^2$ and $I^2$ statistics presented by Review Manager 5.3.4, with $I^2$ further categorized by the tentative Higgins *et al.* heterogeneity categories of: low, moderate and high.[22] The meta-analysis performed calculated the mean intervention effect across all eligible studies using (after analysis of heterogeneity) a random effects model as described by DerSimonian and Laird.[23] An estimate of between-study variation was provided by the Mantel-Haenszel methodology.[24] The main outcome reported for each endpoint is the pooled mean risk ratio (RR), with the pooled mean odds ratio (OR) also presented. In both cases, the 95% confidence interval is specified to allow assessment of result significance.

Sensitivity analyses were specified *a priori* and the tested conditions were: (1) inclusion of high-quality studies only, (2) inclusion of only moderate sedation, (3) inclusion of only studies with low risk of bias, (4) inclusion of only studies based in the US, (5) inclusion of only studies based in Europe, (6) exclusion of pediatric data, (7) exclusion of gender-specific studies, (8) exclusion of data in patients <30 years of

age. No formal statistical comparisons were made between sensitivity analyses, and intervention effects were not calculated for the excluded studies, thereby mitigating the introduction of type 1 error into the analysis.

**Patient involvement**

No patients, service users, carers or lay people were involved in the design or conduct of this study. Outcome measures were all related to patient safety during PSA, but were not developed based on an explicit elicitation of patient priorities, experience, and preferences.

## RESULTS

Literature searches of PubMed, the Cochrane Library and EMBASE returned 385, 87, and 804 articles, respectively. After removal of 270 duplicates (62 Cochrane, 208 EMBASE), 1,006 articles remained for abstract screening. Although reasons for exclusion varied (Supplementary Table 2), the two independent reviewers agreed upon a total of 24 articles to be retained for full-text review (Cohen's kappa, 1.0). Eleven articles were excluded on full-text review (Supplementary Figure 2) because they: reported duplicate data (n=5), did not report patient safety data (n=3), did not include sedation (n=2), or compared two different capnography monitors (n=1). The 13 articles included for analysis are presented in Table 1 and included data on 14 patient groups (one study, published by Mehta *et al.*, provided separate data on colonoscopy and esophagogastroduodenoscopy).[25] All studies reported desaturation endpoints, although the definition did vary by study (Supplementary Table 3). Other endpoints were heterogeneously reported, but were in most cases reported by ≥3 studies making meta-analysis feasible as per the pre-defined protocol. Results reported are from random-effects models unless otherwise stated. Results for hypotension and use of supplemental oxygen are provided in the Supplement.

**Mild desaturation**

All studies (Table 1) reported mild desaturation, with the definition varying from an oxygen saturation ($SpO_2$) of <95% to <90% for ≥15 seconds.[5,6,25,26,27,28,29,30,31,32,33,34,35] There was evidence of heterogeneity ($I^2$ = 50%, moderate) in the primary analysis. Results indicated that capnography significantly reduced the incidence of mild desaturation (RR 0.77, 95% CI 0.67–0.89; OR = 0.67, 95% CI 0.55–0.82; Figure 1). The odds of a mild desaturation event were reduced by over 30% when capnography monitoring is used, compared with no use of capnography. If only high-quality studies (n=7, 8 populations) were included (Supplementary Figure 3), there was evidence of heterogeneity ($I^2$ = 61%, moderate) but the outcome did not differ: RR 0.75 (95% CI 0.62–0.92; OR 0.63, 95% CI 0.48–0.83). Using exclusively studies with equivalent definitions of mild desaturation (<90%, n=8, 9 populations), evidence of heterogeneity ($I^2$ = 57%, moderate) was still present; the RR estimated from these studies was 0.76 (95% CI 0.65–0.89; OR 0.64, 95% CI 0.51–0.80).

**Severe desaturation**

Seven studies, of which four were classified as high quality, reported severe desaturation.[5,25,27–30,34] All but one of the studies defined severe desaturation as $SpO_2$ </≤85%. The analysis for this endpoint was aligned with the significant reduction in the odds of mild desaturation with the inclusion of capnography, with a RR of 0.59 (95% CI 0.43–0.81) and OR of 0.55 (95% CI 0.38–0.78). As with mild desaturation, there was evidence of heterogeneity ($I^2$ = 47%, moderate).

Synthesizing estimates from high-quality studies supported the analysis of all studies, the RR (0.57 95% CI 0.36–0.92) and OR of 0.53 (95% CI 0.31–0.89) reducing by 0.02 and the confidence intervals widening (Supplementary Figure 4). There was moderate heterogeneity between studies ($I^2$ = 64%, moderate). Focusing on the six studies reporting an endpoint of SpO2 </≤85%, there was moderate heterogeneity and the RR was estimated at 0.56 (95% CI 0.41–0.78). Overall, a 40% reduction in the incidence of severe desaturation events would be expected with the use of capnography monitoring relative to standard of care.

**Bradycardia**

Six studies, three of high-quality, reported bradycardia outcomes.[25,28–30,33,34] The definition of bradycardia (heart rate <50 beats/minute) was consistent among five of the six trials and there was no evidence of heterogeneity between the studies ($I^2$ = 0%, low). In four studies, the incidence of bradycardia was higher in the capnography arm compared with the control arm and overall, capnography monitoring was associated with a non-significant increase in bradycardia (RR 1.15, 95% CI 0.89–1.48; OR 1.16, 95% 0.88–1.54) and outcomes were not affected by the inclusion of only high-quality studies or only studies with low risk of bias (Supplementary Figure 7).

**Apnea**

Apnea was less widely reported or reported in combination with disordered respiration. Comparable endpoints were reported in five studies, of which three were high quality.5[6,25,33,34] There was substantial heterogeneity in the apnea outcomes ($I^2$ = 92%, high) and the analysis yielded a non-significant RR of 1.17 (95% CI 0.72–1.89). In an analysis including exclusively high-quality studies, the RR favored capnography but remained non-significant at 0.89 (95% CI 0.64–1.23; Supplementary Figure 8).

There was one clear outlier in the apnea analysis, with data from Klare *et al.* 2016 reporting a RR of 11.71 (95% CI 5.30–25.90).[34] Apnea in this study was undefined for the standard of care arm, but in the capnography arm the apnea criterion was the absence of exhaled $CO_2$ for ≥15 seconds. Different criteria between trial arms may explain the large difference in detected apnea, and capnography would be expected to detect apnea earlier than standard of care monitoring. Excluding this study from the analysis resulted in a RR of 0.85 (95% CI 0.65–1.12; OR 0.73, 95% CI 0.43–1.24).

**Assisted ventilation**

Only one study reported "respiratory failure", which was treated with assisted bag-mask ventilation.[28] In contrast, the number of studies (n=6) reporting assisted and/or bag-mask ventilation was sufficient to perform a meta-analysis of this endpoint as a surrogate for respiratory failure.[5,28,29,31,32,34] Due to the low number of events, a Peto fixed-effects odds-ratio model was used to assess this endpoint.

Analysis found no evidence of heterogeneity ($I^2$ = 0%, low) and demonstrated a significant reduction in assisted ventilation with capnography monitoring (OR 0.47, 95% CI 0.23–0.95). In every case, the need to provide assisted ventilation was lower in the capnography arm compared with the control arm (Figure 2). Three studies were of high-quality and had a low risk of bias, meta-analysis of these studies gave an OR of 0.56 (95% CI 0.27–1.20). Three studies specified assisted ventilation as bag-mask ventilation, and for this subset of studies the OR was 0.56 (95% CI 0.26–1.25).

**Sensitivity analyses**

A series of sensitivity analyses were conducted in which the studies included in the estimation of the RR and OR were varied. The results of these analyses are presented in Table 2 and show that results were generally robust to the studies included for data synthesis. There were limited data available to assess the impact of capnography monitoring during moderate sedation.

## DISCUSSION

The findings of this meta-analysis of recent RCTs comparing visual assessment of ventilation and pulse oximetry monitoring with and without capnography during PSA showed that the odds of oxygen desaturation and assisted ventilation events were significantly reduced with the use of capnography. Other endpoints that could be affected by capnography monitoring were also considered but no significant differences were detected. Of potential clinical importance, was the consistency of data across multiple high-quality clinical trials reporting a reduced incidence of assisted ventilation with capnography monitoring. No endpoints assessed in the meta-analysis indicated significant patient safety concerns with capnography.

Physician concerns for patient safety often focus on mortality and severe morbidity. Using the need for assisted ventilation as a proxy, there was evidence that severe morbidity may differ between control and capnography arms in the present meta-analysis. The incidence of mortality and severe morbidity events during nurse-administered PSA has been reported to be 1 event per 303 procedures (0.33%).[36] Taking this value and using the assumption that capnography could prevent 50% of events

(in line with the estimate from our analysis) and employing trial-size estimation methodology reported by Zhong (2009) showed that 27,726 patients would be required to demonstrate statistical superiority.[37] Switching to an assumption that capnography would prevent 10% of events, the required enrollment would be >900,000 patients. The feasibility of performing such a superiority trial is low, leaving meta-analyses such as the present study as the only viable alternative for determining the impact of capnography on such critical patient endpoints.

The analysis is timely given the ongoing debate as to whether the addition of capnography to patient monitoring during PSA adds value.[17] Without doubt, potential technical and financial burdens have further limited adoption of capnography monitoring in various clinical settings.[15,17] Nevertheless, it is important to recognize that patient safety benefits may offset a number of these concerns if the outcomes are applicable to current medical practice.[38] In this regard, the 13 trials identified in the present analysis were all recent, with the first published study identified in 2006. The data used in the meta-analysis therefore represents modern medical practice, and provides consistent evidence of improvements in patient safety with the use of capnography monitoring.

These findings further substantiate a previously published meta-analysis (Waugh *et al.*), which found that capnography monitoring was more likely to detect adverse events, but was faulted for large endpoint heterogeneity.[16] In the present meta-analysis, we focused on identifying high-quality studies, and on maintaining consistent definitions across all included studies. The results show that the addition of capnography to patient monitoring during PSA results in increased patient safety, with significant reductions in mild and severe levels of oxygen desaturation, as well as the need for assisted ventilation.

A recent meta-analysis by Conway *et al.* reported a significant benefit with capnography during colonoscopy only with respect to hypoxemia. However, the study identified and screened only a fraction of the literature included in the present analysis (388 papers in Conway *et al.*, compared with 1,006 papers in the current study) and retrieved fewer randomized controlled trials (6 versus 13). In addition, Conway *et al.* excluded two trials in which an independent observer monitored capnography

output for all patients, and signaled to the attending physician when respiratory compromise was identified with capnography either immediately (intervention) or after a specified delay (control).5'6 The rationale for this study design was to prevent unnecessary patient harm while avoiding investigator bias. Based on our understanding, the two trials excluded in the Conway *et al.* analysis were the only studies in the literature that could be considered fully blinded. Among the other studies, the attending physician would have been aware of study arm assignment.[27,29,32]

As with other major assessment tools such as Delphi, Consort, and the Cochrane risk of bias tool, blinding is an integral part of the Jadad score used in the present analysis.[19,39] The trials excluded from the Conway *et al.* analysis are both considered to be "high quality" in the present analysis, driven in part by the inclusion of blinding in the scoring methodology. Other included trials, though potentially more representative of current clinical practice, are open to operator bias, the consequences of which were demonstrated in 2012 by Veerus *et al.*[40]

The Jadad score is a widely used score of clinical study quality.[41] In the present analysis, the scale was modified to make it more applicable to monitoring studies by including parameters such as monitoring staff and procedure location. One potential limitation of the present quality appraisal approach was the lack of validation of the modifications to the Jadad score; however, as might have been anticipated, the modified score does significantly correlate with the raw Jadad score (adjusted $R^2 = 0.93$, $p < 0.01$). Furthermore, analysis of mild desaturation data using a mixed model that took the Jadad score or the modified Jadad score as a covariate, found no significant difference between models and the heterogeneity accounted for (approximately 50% for both models).

Another ongoing debate in PSA concerns the clinical importance of seemingly minor endpoints, such as mild desaturation (oxygenation <90% for 15 seconds). Although such endpoints have traditionally been considered transient and perhaps clinically insignificant during PSA, several recent studies of common intraoperative events have suggested that mild desaturation may have more impact on post-surgical outcomes than has previously been recognized.[42] For example, Dunham *et al.* looked retrospectively and determined that surgical patients who experienced perioperative

hypoxemia/desaturation had a significant increase in their length of hospital stay (+2.0 days, p<0.0001).[43] In turn, the impact of transient desaturation during PSA in terms of patient outcomes and quality of life may yet be of importance but remains to be determined.

Over all the studies included in the analysis, there was one report of patient mortality, in the standard of care arm of the trial presented by Klare *et al.*, 2016.[34] Only the largest trials reported any requirement for assisted/bag-mask ventilation, which is used as an intervention and thereby a proxy measure for potentially life-threatening events. Although it is generally accepted that much larger studies would be useful to assess whether or not capnography monitoring impacts patient major morbidity and mortality, there has been no determination of the trial size that would be required. Power calculations suggest such a large randomized controlled trial is likely to be impractical.

For healthcare providers, the most significant finding may be the consistency of data surrounding assisted ventilation and severe oxygen desaturation with capnography. Two closed claim reviews both found that inadequate oxygenation/ventilation was the most frequent event leading to a claim related to PSA outside the operating room.[44,45] The potential cost burden is demonstrated by the median cost of a claim settled being USD 330,000 (in 2007 USD).[44] The authors reported that better monitoring would have reduced the number of claims.[44] A similar message was returned following the fourth National Audit Project in the UK, which analyzed major complications of airway management in the National Health Service and determined that capnography monitoring could have led to earlier identification of airway obstruction, potentially preventing 74% of death or neurological injury cases.[46,47] Studies included in the present meta-analysis reported that disordered ventilation as detected by capnography preceded desaturation events by 30 to 60 seconds.

The meta-analysis did find an increase in bradycardia with capnography monitoring that was non-significant. However, in each of the trials reporting higher incidence the patients in the capnography arm had larger doses and increased use of multiple agents for inducing PSA. Such confounding is plausible, may not be unusual, and was discussed as possible factor in the trial outcomes by Campbell *et al.* 2016.[48] All other findings of the current analysis were in line with expectations around

the potential benefits of capnography; as further substantiated by the results of our meta-analysis, earlier identification of respiratory compromise appears to result in more timely intervention and prevention of its escalation into patient harm.

As with all data synthesis projects, the present study is only as accurate and reliable as the data underlying it. In the literature, there are examples of newly-published clinical trials that do not align with the results of published meta-analyses, and meta-analysis results changing on the publication of new data.[49,50] The systematic nature of study identification and inclusion criteria in the present analysis was designed to identify all available literature and provide the most robust estimates of intervention effect. However, the included studies came from a variety of hospital settings, in which the rate of patient safety events might vary. This is apparent in the clinical trial results presented by Mehta *et al.*, where colonoscopy and esophagogastroduodenoscopy were assessed independently due to differences in outcomes.[25] Analyses for particular settings were undertaken, but were then limited by reduced data availability. In total, this analysis represented 5,460 patients (control 2,755 and capnography 2,705) over 13 studies. Between trials, the number of patients enrolled varied between 132 and 986. Notably, of the six studies that identified rare outcomes, such as differences in use of assisted ventilation, five enrolled >500 patients.

## CONCLUSIONS

The results of this comprehensive meta-analysis of clinical trials provide clear and consistent evidence of decreased respiratory compromise when capnography monitoring is used during procedural sedation and analgesia (PSA). Specifically, the analysis identified a statistically significant and clinically meaningful reduction in mild and severe oxygen desaturation, as well as in assisted ventilation. Large, well designed, randomized controlled trials to provide direct links between use of capnography and reduction in patient harm may not be feasible. In turn, calls for this type of primary evidence may delay adoption of capnography monitoring during PSA as a valuable tool for early intervention and improved patient safety.

**Word Count** 5,233

## AUTHOR CONTRIBUTIONS

MM formulated the research question; RFP and RS devised the search strategy and data extraction protocol, which was critically reviewed and revised by MM, JRL and MMRFS; RFP and RS then conducted the literature searches, screening, data extraction, and meta-analysis, and co-wrote the manuscript; MM, JRL and MMRFS critically reviewed the manuscript and made substantive revisions prior to submission.

## DATA SHARING STATEMENT

All data used to derive the outcomes presented in the study are documented in the manuscript and supplementary materials. No additional data are therefore available.

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## TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been

omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## ETHICAL APPROVAL

No ethical approval was required for the study as all data were derived from published data; neither animal nor human subjects were enrolled as part of the present study.

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## FINANCIAL AND COMPETING INTEREST DISCLOSURE

All authors have completed the Unified Competing Interest forms at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

- Michael Mestek is a full-time employee of Medtronic plc.
- Richard F Pollock is a full-time employee of Ossian Health Economics and Communications GmbH, which received research and consultancy fees from Medtronic plc. to conduct the literature review and meta-analysis and prepare the manuscript.
- Rhodri Saunders was a full-time employee of Ossian Health Economics and Communications GmbH at the time of performing the meta-analysis and is currently a director of Coreva Scientific GmbH & Co. KG.
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- Jenifer R Lightdale has served as a consultant for Medtronic and Norgine, and has received speaker honorarium from Mead-Johnson and Perrigo.

## TABLES AND FIGURES

**Table 1 Included studies reporting endpoints of interest**

| Study (reference) | Country | Trial dates | Modified Jadad † | Potential for bias | Hospital setting | Depth of sedation | Sedative | Monitoring staff | Oxygen at baseline | N (control, Cap) |
|---|---|---|---|---|---|---|---|---|---|---|
| Beitz 2012[28] | Germany | Feb-10, Jan-11 | 5.5 | High: 3 | Colonoscopy | "adequate" | Propofol | Not specified | 2 L/minute | 757 (374, 383) |
| Deitch 2010[26] | US | Nov-06, Feb-08 | 5.5 | Low: 0 | Emergency department | Moderate | Propofol | Not specified | 3 L/minute | 132 (64, 68) |
| Friedrich-Rust 2014[29] | Germany | Jun-12, May-13 | 6 | Low: 0 | Colonoscopy | Deep | Propofol+ | Anesthesiologist or sedation-trained nurse | 2 L/minute | 533 (266, 267) |
| Langhan 2015[31] | US | Sep-11, Jan-13 | 6 | Low: 0 | Pediatric emergency department | NA | Ketamine, midazolam | "Treating staff" | None | 154 (77, 77) |
| Lightdale 20066 | US | Dec-03, Nov-04 | 8 | Low: 0 | Endoscopy | Moderate | Fentanyl, midazolam | Independent observer | 2 L/minute | 163 (80, 83) |
| Qadeer 20095 | US | Jan-07, May-08 | 7.5 | Moderate: 1 | ERCP and EUS | NA | Midazolam+ | Independent observer | None | 247 (124, 123) |
| Slagelse 2013[32] | Denmark | Sep-10, Jan-11 | 6 | Low: 0 | Endoscopy | NA | Propofol | Sedation-trained nurse | 2-3 L/minute | 540 (277, 263) |
| van Loon 2014[27] | Netherlands | Apr-10, Jan-11 | 5 | Low: 0 | Gynecology | Deep | Propofol | Medical team providing sedation | None | 415 (209, 206) |
| Zongming 2014[30] | China | Nov-10, May-13 | 6 | Low: 0 | Abortion | Deep | Propofol | Anesthesiologist | 3 L/minute | 700 (359, 341) |
| Campbell 2016 | Canada | Apr-06, Apr-12 | 5 | Moderate: 2 | Emergency department | NA | Physician's choice | Paramedic acute care practioner | 98.7% received oxygen | 986 (501, 485) |
| Klare 2016[34] | Germany | Feb-10, Oct-11 | 5.5 | Moderate: 1 | ERCP | Deep | Midazolam and | Physician not | 2 L/minute | 238 (117, 121) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | propofol | performing procedure | | |
| Mehta 2016 (colon)[25] | US | Dec-13, Jan-15 | 8 | Low: 0 | Colonoscopy | Moderate | Fentanyl or meperidine, plus midazolam | Independent observer | None | 231 (114, 117) |
| Mehta 2016 (EGD)[25] | US | Dec-13, Jan-15 | 8 | Low: 0 | EGD | Moderate | Fentanyl or meperidine, plus midazolam | Independent observer | None | 209 (108, 101) |
| Riphaus 2016[33] | Germany | Jun-10, Nov-11 | 5.5 | High: 3 | EUS | "adequate" | Midazolam and propofol | Independent observer | 2 L/minute | 170 (87, 83) |

† Higher scores indicate higher quality studies. In the present analysis, a score of 6.0–8.0 was designated as high quality.
+, in combination with multiple other agents; BZP, benzodiazepine; Cap, Capnography (arm); EGD, Esophagogastroduodenoscopy; ERCP, Endoscopic retrograde cholangiopancreatography; EUS, Endoscopic ultrasonography

**Figure 1 Severe and mild desaturation are significantly reduced with capnography monitoring**

The risk ratios for the endpoints of mild desaturation (A) and severe desaturation (B) are presented. CI, Confidence interval; M-H, Mantel-Haenszel

**Figure 2 The need for assisted ventilation is reduced with capnography monitoring**

]The odds ratios for the assisted ventilation endpoint are presented for all studies (A), high quality studies (B), studies with low risk of bias (C), and studies with the end point specified as bag-mask ventilation (D). CI, Confidence interval; M-H, Mantel-Haenszel

**Table 2** **Sensitivity analyses around the primary analyses**

| Scenario | Desaturation, mild | Desaturation, severe | Apnea | Bradycardia | Hypotension | Assisted ventilation | Supplemental oxygen |
|---|---|---|---|---|---|---|---|
| **Base case (all studies)** | **0.77 [0.67, 0.89]** | **0.59 [0.43, 0.81]** | **1.17 [0.72, 1.89]** | **1.16 [0.88, 1.54]** | **1.02 [0.78, 1.33]** | 0.47 [0.23, 0.95] | **0.93 [0.75, 1.15]** |
| High quality studies | 0.75 [0.62, 0.92] | 0.57 [0.36, 0.92] | 0.89 [0.64, 1.23] | 1.26 [0.80, 1.99] | 0.97 [0.73, 1.30] | 0.56 [0.27, 1.20] | 0.98 [0.79, 1.23] |
| Moderate sedation | 0.80 [0.60, 1.07] | - | 0.99 [0.69, 1.42] | - | - | - | - |
| US only | 0.80 [0.64, 0.99] | 0.59 [0.26, 1.30] | 0.89 [0.64, 1.23] | - | 1.04 [0.57, 1.88] | - | - |
| Europe only | 0.77 [0.63, 0.96] | 0.61 [0.44, 0.84] | 2.83 [0.12, 67.30] | 1.18 [0.86, 1.61] | 0.90 [0.66, 1.24] | 0.49 [0.23, 1.03] | 0.91 [0.67, 1.25] |
| Studies with potential bias excluded | 0.78 [0.64, 0.95] | 0.65 [0.37, 1.14] | 0.99 [0.69, 1.42] | 1.26 [0.80, 1.99] | 0.92 [0.68, 1.25] | 0.56 [0.27, 1.20] | 1.16 [0.95, 1.41] |
| Studies in pediatrics excluded | 0.78 [0.67, 0.89] | 0.59 [0.43, 0.81] | 1.29 [0.75, 2.23] | 1.16 [0.88, 1.54] | 1.02 [0.78, 1.33] | 0.47 [0.23, 0.95] | 0.92 [0.74, 1.14] |
| Gender-specific studies excluded | 0.76 [0.66, 0.89] | 0.59 [0.41, 0.84] | 1.17 [0.72, 1.89] | 1.18 [0.84, 1.65] | 1.03 [0.75, 1.41] | 0.49 [0.23, 1.03] | 0.84 [0.68, 1.03] |
| Studies with mean age >30 years | 0.75 [0.65, 0.87] | 0.56 [0.41, 0.78] | 1.29 [0.75, 2.23] | 1.16 [0.88, 1.54] | 1.02 [0.78, 1.33] | 0.47 [0.23, 0.95] | 0.87 [0.71, 1.07] |

The reported treatment effect is the relative risk (RR) [95% confidence interval], except for assisted ventialtion where the peto odds ratio (OR) [95% confidence interval] is used.

CI, confidence interval; US, United States

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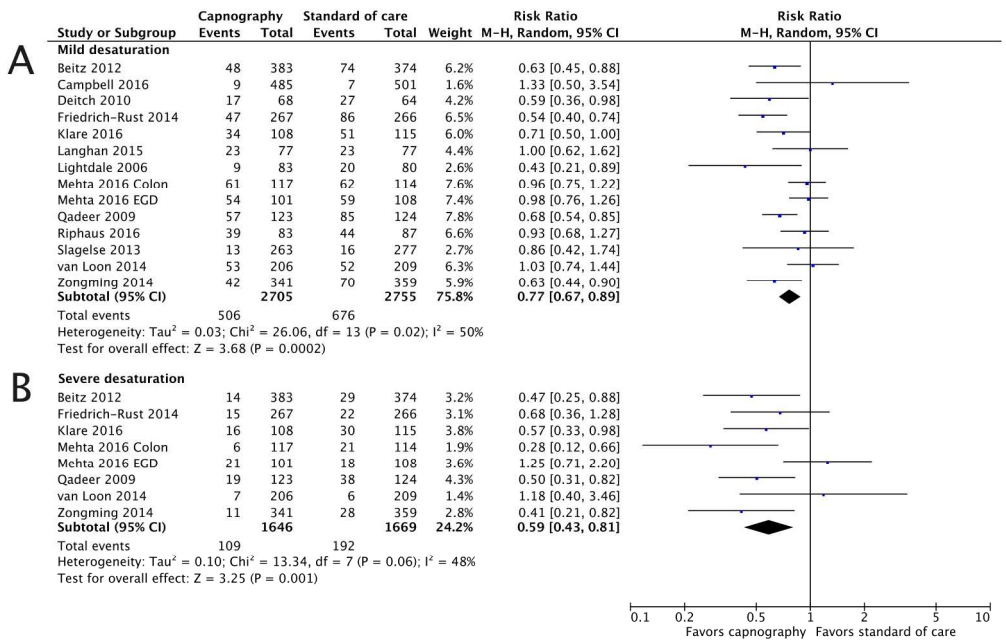
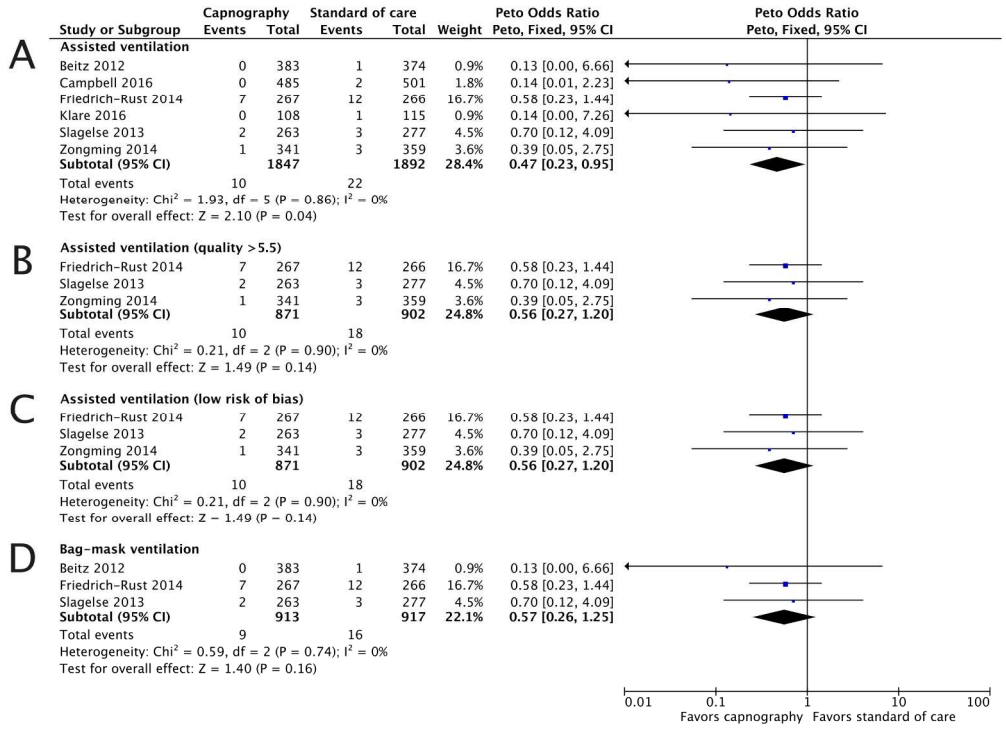



Severe and mild desaturation are significantly reduced with capnography monitoring
Figure 1
205x132mm (300 x 300 DPI)




The need for assisted ventilation is reduced with capnography monitoring
Figure 2
205x152mm (300 x 300 DPI)

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 22 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 22 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 23 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 19,24 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 16 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 17,24-27 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 17,24-27 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 18 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 18 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12-13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 14 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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# PATIENT SAFETY DURING PROCEDURAL SEDATION USING CAPNOGRAPHY MONITORING: A SYSTEMATIC REVIEW AND META-ANALYSIS



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# PATIENT SAFETY DURING PROCEDURAL SEDATION USING CAPNOGRAPHY MONITORING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

### Objective

To evaluate the effect of capnography monitoring on sedation-related adverse events during procedural sedation and analgesia (PSA) administered for ambulatory surgery relative to visual assessment and pulse oximetry alone.

### Design and Setting

Systematic literature review and random effects meta-analysis of randomized controlled trials (RCTs) reporting sedation-related adverse event incidence when adding capnography to visual assessment and pulse oximetry in patients undergoing PSA during ambulatory surgery in the hospital setting. Searches for eligible studies published between January 1, 1995 and December 31, 2016 (inclusive) were conducted in PubMed, the Cochrane Library and EMBASE without any language constraints. Searches were conducted in January 2017, screening and data extraction were conducted by two independent reviewers, and study quality was assessed using a modified Jadad scale.

### Interventions

Capnography monitoring relative to visual assessment and pulse oximetry alone.

### Primary and Secondary Outcome Measures

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA.

### Results

The literature search identified 1,006 unique articles, of which 13 were ultimately included in the meta-analysis. Addition of capnography to visual assessment and pulse oximetry was associated with a significant reduction in mild (risk ratio [RR] 0.77, 95% CI 0.67–0.89) and severe (RR 0.59, 95% CI 0.43–

0.81) desaturation, as well as in the use of assisted ventilation (odds ratio 0.47, 95% CI 0.23–0.95). No significant differences in other endpoints were identified.

**Conclusions**

Meta-analysis of 13 RCTs published between 2006 and 2016 showed a reduction in respiratory compromise (from respiratory insufficiency to failure) during PSA with the inclusion of capnography monitoring. In particular, use of capnography was associated with less mild and severe oxygen desaturation, which may have helped to avoid the need for assisted ventilation.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

**Strengths**

- The studies included in the analysis were all published in 2006 or later, representing modern medical practice and providing clinically relevant evidence of improvements in patient safety with the use of capnography monitoring.
- The study findings further substantiate a previously published meta-analysis, which found that capnography monitoring was more likely to detect adverse events. It also suggests that superior detection may reduce the use of clinical interventions intended to rescue patients from potential adverse outcomes.

**Limitations**

- The level of sedation employed in each study was not uniformly reported, resulting in a mixture of different sedation levels in the primary analysis and precluding an analysis of outcomes by sedation level.
- As with all meta-analyses, the study findings may be affected by publication, search or selection bias affecting the studies ultimately included in the analysis. Where possible, steps were taken to minimize the effects of bias on the analysis, but the degree to which these steps were successful is difficult to quantify.

## BACKGROUND AND AIMS

The administration of procedural sedation and analgesia (PSA) involves achieving a drug-induced depression in level of consciousness and pain to ensure the comfort and cooperation of patients undergoing non-surgical and minor surgical procedures. Significant adverse events associated with PSA are relatively rare but not inconsequential, and can include severe oxygen desaturation, bradycardia, hypotension, and cardiac arrest.[1,2] Consensus dictates that levels of sedation are directly related to patient risk during PSA, as is the potential for unintended progression from moderate to deep sedation.[3] Generally speaking, most cardiopulmonary events associated with PSA stem from poor or absent ventilation cascading into hypoxia, tissue injury and cardiac decompensation (Supplementary Figure 1). In turn, maintaining patient safety involves the identification of respiratory compromise to prompt the use of clinical intervention before further complications occur.[4,5,6,7,8,9]

In current clinical practice, patient monitoring during PSA often relies on visual assessment of ventilation and use of pulse oximetry, which reflects hypoxemia.[10,11,12,13,14] To date, a mandate to include capnography in patient monitoring, as a means of early detection of alveolar hypoventilation, has remained a topic of debate.[15] In particular, there has been a perceived gap between various study outcomes and evidence of improved patient safety. No studies have provided "hard proof" that addition of capnography to patient monitoring may reduce severe morbidity and mortality during PSA (in part because of ethical considerations to ensure patient rescue). Previous efforts to use meta-analysis to determine the utility of capnography to identify clinically significant respiratory depression have been faulted for large heterogeneity and non-standard endpoints.[16,17]

The primary aim of the present systematic review and meta-analysis was to understand whether capnography added to patient monitoring only (consisting of pulse oximetry and visual inspection of ventilation) reduces the incidence (or odds) of adverse events during PSA based on randomized controlled trials of patients undergoing a variety of surgical procedures. The analysis was based on the hypothesis that earlier and more sensitive detection of ventilatory changes with capnography may

allow for more timely intervention and prevention of potential adverse events, such as cardiac dysrhythmias. Throughout the analyses, we sought to provide the highest level of synthesized evidence with respect to the clinical utility of capnography monitoring during PSA. To mitigate potential pitfalls due to non-standard endpoints, particular emphasis was placed on maintaining a consistent definition of adverse events across all studies included.

## METHODS

Literature searches were conducted in PubMed, the Cochrane Library and EMBASE. Search terms were a combination of Medical Subject Heading (MeSH) terms and free-text searches within the articles title and abstract. Searches aimed to identify all literature reporting on randomized, controlled trials in patients receiving sedation during ambulatory surgery and in which visual assessment of ventilation and pulse oximetry monitoring (control) was compared with control plus capnography. "Grey" or unpublished literature (including congress abstracts) was included in the search strategy and, as the review protocol was not registered in advance, the full search strategy (Supplementary Table 1) and additional details are provided in the Supplement. Only articles or abstracts published on or after January 1, 1995 were included and all searches were performed on January 15, 2017. A previous systematic review in this area did not identify any study prior to 1995,[16] and studies published prior to 1995 were considered unlikely to reflect modern clinical practice. No language exclusion was applied and inclusion was not dependent on the capnography monitor in use. After duplicate removal, title and abstract screening (Supplementary Table 2) was performed independently by RS and RFP using Sourcerer (Covalence Research Ltd, London UK).[18] Full-text versions of all non-excluded articles were retrieved by MM and reviewed independently by RS and RFP. Data were then extracted independently by RS and RFP into data extraction forms in Microsoft Excel (Microsoft Corporation, Redmond, WA). Any discrepancies in the extracted data were resolved by reference to the original study, reaching consensus between RS and RFP. All extracted endpoint data were reviewed by JL and MMS for clinical utility to ensure that all synthesized data relate to clinically equivalent endpoints. Extracted data

included the number of patients with events and the population at risk, in addition to items required to assess article quality and bias. Reference lists of included studies were not searched.

**Endpoints**

Predefined endpoints of interest were desaturation/hypoxemia (the primary endpoint, with severe desaturation defined as $SpO_2$ ≤85%), apnea, aspiration, bradycardia, hypotension, premature procedure termination, respiratory failure, use of assisted/bag-mask ventilation and death during PSA. The protocol was left open for the analysis of other patient safety endpoints that were reported by ≥3 studies. Cardiac arrest and death were considered to be representative of severe morbidity and mortality. Notably, the present analysis examined individual endpoints as opposed to composite endpoints (e.g. desaturation, apnea, or respiratory depression) and included analyses of more specific endpoints, such as oxygen desaturation <90% and <85%.

**Quality and potential bias**

Assessment of article quality was conducted on a study (as opposed to outcome) level using a modified Jadad score,[19] with additional criteria added to make the adaptation specific to monitoring. The Jadad score assesses studies based on their design (randomized and blinded) and their reporting (all patients accounted for), with a maximal score of 5 (high quality) and a low score of 0 (low quality). Additional data included here were endpoint definitions, patient population, hospital location at which patients underwent sedation, and the staff responsible for monitoring. In line with the Jadad score, items related to trial design could score up to twice as highly as items relating to trial reporting. The reporting of the inclusion/exclusion criteria and endpoint definitions scored one point each, and reporting the location of sedation, and the monitoring staff scored half-point point each, making the maximal score 8 (high quality). For the purposes of analyzing study quality, studies with scores of 0–5.5 were considered to be low quality, while studies scoring 6.0–8.0 were designated as high-quality studies.

Risk of bias in results was evaluated independently from the quality assessment through the declaration of funding sources and conflicts of interest. If the study was funded by industry then the study scored 2, any conflicts of interest declared relating to industry funding outside of the current research publication scored 1. A study with low potential for bias, therefore, would have a score of 0. A high potential for bias was defined as a score of 3, while a score of 1–2 was considered to indicate moderate potential for bias. The absence of industry funding was not taken to signify an absence of bias, but the presence of industry funding or conflicts of interest was assumed to be an indicator of bias.[20]

**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.[21] Heterogeneity of data was evaluated using $Chi^2$ and $I^2$ statistics presented by Review Manager 5.3.4, with $I^2$ further categorized by the tentative Higgins *et al.* heterogeneity categories of: low, moderate and high.[22] The meta-analysis performed calculated the mean intervention effect across all eligible studies using (after analysis of heterogeneity) a random effects model as described by DerSimonian and Laird.[23] An estimate of between-study variation was provided by the Mantel-Haenszel methodology.[24]

The main outcome reported for each endpoint was the pooled mean risk ratio (RR), except when the incidence of rare endpoints was less than 1%. In these instances, the Peto method was used as a fixed-effects model designed specifically for analysis of rare endpoints. The Peto method only reports an odds ratio (OR) and, to allow comparison between all endpoints analyzed, the pooled mean OR was therefore also presented for all analyses. In all cases, the 95% confidence interval is reported to allow assessment of significance.

Sensitivity analyses were specified *a priori* and the tested conditions were: (1) inclusion of high-quality studies only, (2) inclusion of only moderate sedation, (3) inclusion of only studies with low risk of bias,

(4) inclusion of only studies based in the US, (5) inclusion of only studies based in Europe, (6) exclusion of pediatric data, (7) exclusion of gender-specific studies, (8) exclusion of data in patients <30 years of age. No formal statistical comparisons were made between sensitivity analyses, and intervention effects were not calculated for the excluded studies, thereby mitigating the introduction of type 1 error into the analysis.

**Patient involvement**

No patients, service users, or lay people were involved in the design or conduct of this study. Outcome measures were all related to patient safety during PSA, but were not developed based on an explicit elicitation of patient priorities, experience, and preferences.

## RESULTS

Literature searches of PubMed, the Cochrane Library and EMBASE returned 385, 87, and 804 articles, respectively. After removal of 270 duplicates (62 Cochrane, 208 EMBASE), 1,006 articles remained for abstract screening. Although reasons for exclusion varied (Supplementary Table 2), the two independent reviewers agreed upon a total of 24 articles to be retained for full-text review (Cohen's kappa, 1.0). Eleven articles were excluded on full-text review (Supplementary Figure 2) because they: reported duplicate data (n=5), did not report patient safety data (n=3), did not include sedation (n=2), or compared two different capnography monitors (n=1). The 13 articles included for analysis are presented in Table 1 and included data on 14 patient groups (one study, published by Mehta *et al.*, provided separate data on colonoscopy and esophagogastroduodenoscopy).[25] All studies reported desaturation endpoints, although the definition did vary by study (Supplementary Table 3). Other endpoints were heterogeneously reported, but were in most cases reported by ≥3 studies making meta-analysis feasible as per the pre-defined protocol. Results reported are from random-effects models unless otherwise stated. Results for hypotension and use of supplemental oxygen are provided in the Supplement.

**Mild desaturation**

All studies (Table 1) reported mild desaturation, with the definition varying from an oxygen saturation ($SpO_2$) of <95% to <90% for ≥15 seconds.[5,6,25,26,27,28,29,30,31,32,33,34,35] There was evidence of heterogeneity ($I^2$ = 50%, moderate) in the primary analysis. Results indicated that capnography significantly reduced the incidence of mild desaturation (RR 0.77, 95% CI 0.67–0.89; OR = 0.67, 95% CI 0.55–0.82; Figure 1). The odds of a mild desaturation event were reduced by over 30% when capnography monitoring is used, compared with no use of capnography. If only high-quality studies (n=7, 8 populations) were included (Supplementary Figure 3), there was evidence of heterogeneity ($I^2$ = 61%, moderate) but the outcome did not differ: RR 0.75 (95% CI 0.62–0.92; OR 0.63, 95% CI 0.48–0.83). Using exclusively studies with equivalent definitions of mild desaturation (<90%, n=8, 9 populations), evidence of heterogeneity ($I^2$ = 57%, moderate) was still present; the RR estimated from these studies was 0.76 (95% CI 0.65–0.89; OR 0.64, 95% CI 0.51–0.80).

**Severe desaturation**

Seven studies, of which four were classified as high quality, reported severe desaturation.[5,25,27–30,34] All but one of the studies defined severe desaturation as $SpO_2$ </≤85%. The analysis for this endpoint was aligned with the significant reduction in the odds of mild desaturation with the inclusion of capnography, with a RR of 0.59 (95% CI 0.43–0.81) and OR of 0.55 (95% CI 0.38–0.78). As with mild desaturation, there was evidence of heterogeneity ($I^2$ = 47%, moderate).

Synthesizing estimates from high-quality studies supported the analysis of all studies, the RR (0.57 95% CI 0.36–0.92) and OR of 0.53 (95% CI 0.31–0.89) reducing by 0.02 and the confidence intervals widening (Supplementary Figure 4). There was moderate heterogeneity between studies ($I^2$ = 64%, moderate). Focusing on the six studies reporting an endpoint of SpO2 </≤85%, there was moderate heterogeneity and the RR was estimated at 0.56 (95% CI 0.41–0.78). Overall, a 40% reduction in the incidence of severe desaturation events would be expected with the use of capnography monitoring relative to standard of care.

**Bradycardia**

Six studies, three of high-quality, reported bradycardia outcomes.[25,28–30,33,34] The definition of bradycardia (heart rate <50 beats/minute) was consistent among five of the six trials and there was no evidence of heterogeneity between the studies ($I^2$ = 0%, low). In four studies, the incidence of bradycardia was higher in the capnography arm compared with the control arm and overall, capnography monitoring was associated with a non-significant increase in bradycardia (RR 1.15, 95% CI 0.89–1.48; OR 1.16, 95% 0.88–1.54) and outcomes were not affected by the inclusion of only high-quality studies or only studies with low risk of bias (Supplementary Figure 7).

**Apnea**

Apnea was less widely reported or reported in combination with disordered respiration. Comparable endpoints were reported in five studies, of which three were high quality.5[,6,25,33,34] There was substantial heterogeneity in the apnea outcomes ($I^2$ = 92%, high) and the analysis yielded a non-significant RR of 1.17 (95% CI 0.72–1.89). In an analysis including exclusively high-quality studies, the RR favored capnography but remained non-significant at 0.89 (95% CI 0.64–1.23; Supplementary Figure 8).

There was one clear outlier in the apnea analysis, with data from Klare *et al.* 2016 reporting a RR of 11.71 (95% CI 5.30–25.90).[34] Apnea in this study was undefined for the standard of care arm, but in the capnography arm the apnea criterion was the absence of exhaled $CO_2$ for ≥15 seconds. Different criteria between trial arms may explain the large difference in detected apnea, and capnography would be expected to detect apnea earlier than standard of care monitoring. Excluding this study from the analysis resulted in a RR of 0.85 (95% CI 0.65–1.12; OR 0.73, 95% CI 0.43–1.24).

**Assisted ventilation**

Only one study reported "respiratory failure", which was treated with assisted bag-mask ventilation.[28] In contrast, the number of studies (n=6) reporting assisted and/or bag-mask ventilation was sufficient to perform a meta-analysis of this endpoint as a surrogate for respiratory failure.[5,28,29,31,32,34] Due to the

low number of events, a Peto fixed-effects odds-ratio model was used to assess this endpoint. Analysis found no evidence of heterogeneity ($I^2$ = 0%, low) and demonstrated a significant reduction in assisted ventilation with capnography monitoring (OR 0.47, 95% CI 0.23–0.95). In every case, the need to provide assisted ventilation was lower in the capnography arm compared with the control arm (Figure 2). Three studies were of high-quality and had a low risk of bias, meta-analysis of these studies gave an OR of 0.56 (95% CI 0.27–1.20). Three studies specified assisted ventilation as bag-mask ventilation, and for this subset of studies the OR was 0.56 (95% CI 0.26–1.25).

**Sensitivity analyses**

A series of sensitivity analyses were conducted in which the studies included in the estimation of the RR and OR were varied. The results of these analyses are presented in Table 2 and show that results were generally robust to the studies included for data synthesis. There were limited data available to assess the impact of capnography monitoring during moderate sedation.

## DISCUSSION

The findings of this meta-analysis of recent RCTs comparing visual assessment of ventilation and pulse oximetry monitoring with and without capnography during PSA showed that the odds of oxygen desaturation and assisted ventilation events were significantly reduced with the use of capnography. Other endpoints that could be affected by capnography monitoring were also considered but no significant differences were detected. Of potential clinical importance, was the consistency of data across multiple high-quality clinical trials reporting a reduced incidence of assisted ventilation with capnography monitoring. No endpoints assessed in the meta-analysis indicated significant patient safety concerns with capnography.

Physician concerns for patient safety often focus on mortality and severe morbidity. Using the need for assisted ventilation as a proxy, there was evidence that severe morbidity may differ between control and capnography arms in the present meta-analysis. Although we note that no single trial showed a significant difference in this outcome, the information now exists to perform a power

calculation to determine the number of patients that would be required to be enrolled in a prospective clinical trial to demonstrate a significant reduction in patient harm. The incidence of mortality and severe morbidity events during nurse-administered PSA has been reported to be 1 event per 303 procedures (0.33%).[36] Taking this value along with the assumption that capnography could prevent 50% of events (in line with the estimate from our analysis), and employing trial-size estimation methodology reported by Zhong (2009) showed that 27,726 patients would be required to demonstrate statistical superiority..[37] Switching to an assumption that capnography would prevent 10% of events, the required enrollment would be >900,000 patients. As such, we submit the feasibility of performing superiority trials is low, and leaves meta-analyses, such as the present study, as the only viable alternative for determining the impact of capnography on such critical patient endpoints.

Our analysis is timely given the ongoing debate as to whether the addition of capnography to patient monitoring during PSA adds value.[17] Without doubt, potential technical and financial burdens have further limited adoption of capnography monitoring in various clinical settings.[15,17] Nevertheless, it is important to recognize that patient safety benefits may offset a number of these concerns if the outcomes are applicable to current medical practice.[38] In this regard, the 13 trials identified in the present analysis were all recent, with the first published study identified in 2006. The data used in the present meta-analysis therefore represent modern medical practice, and provides consistent evidence of improvements in patient safety with the use of capnography monitoring.

Our findings further substantiate a previously published meta-analysis (Waugh *et al.*), which found that capnography monitoring was more likely to detect adverse events, but was faulted for large endpoint heterogeneity.[16] In the present meta-analysis, we focused on identifying high-quality studies, and on maintaining consistent definitions across all included studies. The results show that the addition of capnography to patient monitoring during PSA results in increased patient safety, with significant reductions in mild and severe levels of oxygen desaturation, as well as the need for assisted ventilation.

A recent meta-analysis by Conway *et al.* reported a significant benefit with capnography during colonoscopy only with respect to hypoxemia. However, the present meta-analysis identified and screened only a fraction of the literature included in the present analysis (388 papers in Conway *et al.*, compared with 1,006 papers in the current study) and retrieved fewer randomized controlled trials (6 versus 13). In addition, Conway *et al.* excluded two trials in which an independent observer monitored capnography output for all patients, and signaled to the attending physician when respiratory compromise was identified with capnography either immediately (intervention) or after a specified delay (control).5'6 The rationale for this study design was to prevent unnecessary patient harm while avoiding investigator bias. Based on our understanding, the two trials excluded in the Conway *et al.* analysis were the only studies in the literature that could be considered fully blinded. Among the other studies, the attending physician would have been aware of study arm assignment.[27,29,32]

As with other major assessment tools such as Delphi, Consort, and the Cochrane risk of bias tool, blinding is an integral part of the Jadad score used in the present analysis.[19,39] The trials excluded from the Conway *et al.* analysis are both considered to be "high quality" in the present analysis, driven in part by the inclusion of blinding in the scoring methodology. Other included trials, though potentially more representative of current clinical practice, are open to operator bias, the consequences of which were demonstrated in 2012 by Veerus *et al.*[40]

The Jadad score is a widely used score of clinical study quality.[41] In the present analysis, the scale was modified to make it more applicable to monitoring studies by including parameters such as monitoring staff and procedure location. One potential limitation of the present quality appraisal approach was the lack of validation of the modifications to the Jadad score; however, as might have been anticipated, the modified score does significantly correlate with the raw Jadad score (adjusted $R^2 = 0.93$, $p < 0.01$). Furthermore, analysis of mild desaturation data using a mixed model that took the Jadad score or the modified Jadad score as a covariate, found no significant difference between models and the heterogeneity accounted for (approximately 50% for both models).

Another ongoing debate in PSA concerns the clinical importance of seemingly minor endpoints, such as mild desaturation (oxygenation <90% for 15 seconds). Although such endpoints have traditionally been considered transient and perhaps clinically insignificant during PSA, several recent studies of common intraoperative events have suggested that mild desaturation may have more impact on post-surgical outcomes than has previously been recognized.[42] For example, Dunham *et al.* looked retrospectively and determined that surgical patients who experienced perioperative hypoxemia/desaturation had a significant increase in their length of hospital stay (+2.0 days, $p<0.0001$).[43] In turn, the impact of transient desaturation during PSA in terms of patient outcomes and quality of life may yet be of importance but remains to be determined.

Over all of the randomized trials included in the analysis, there was one report of patient mortality, which occurred in the standard of care arm of the trial presented by Klare *et al.*, 2016.[34] Only the largest trials reported any requirement for assisted/bag-mask ventilation, which is used as an intervention and thereby a proxy measure for potentially life-threatening events. Although it is widely accepted that much larger studies would be useful to assess whether or not capnography monitoring impacts patient major morbidity and mortality, there has been no determination to date of the trial size that would be required. Power calculations furthered by our meta-analysis suggest such a large randomized controlled trial is likely to be impractical.

For healthcare providers, the most significant finding may be the consistency of data surrounding assisted ventilation and severe oxygen desaturation with capnography. Two closed claim reviews both found that inadequate oxygenation/ventilation was the most frequent event leading to a claim related to PSA outside the operating room.[44,45] The potential cost burden is demonstrated by the median cost of a claim settled being USD 330,000 (in 2007 USD).[44] The authors reported that better monitoring would have reduced the number of claims.[44] A similar message was returned following the fourth National Audit Project in the UK, which analyzed major complications of airway management in the National Health Service and determined that capnography monitoring could have led to earlier identification of airway obstruction, potentially preventing 74% of death or neurological injury

cases.[46,47] Studies included in the present meta-analysis reported that disordered ventilation as detected by capnography preceded desaturation events by 30 to 60 seconds.

The meta-analysis did find an increase in bradycardia with capnography monitoring that was non-significant. However, in each of the trials reporting higher incidence the patients in the capnography arm had larger doses and increased use of multiple agents for inducing PSA. Such confounding is plausible, may not be unusual, and was discussed as possible factor in the trial outcomes by Campbell *et al.* 2016.[48] All other findings of the current analysis were in line with expectations around the potential benefits of capnography; as further substantiated by the results of our meta-analysis, earlier identification of respiratory compromise appears to result in more timely intervention and prevention of its escalation into patient harm.

As with all data synthesis projects, the present study is only as accurate and reliable as the data underlying it. In the literature, there are examples of newly-published clinical trials that do not align with the results of published meta-analyses, and meta-analysis results changing on the publication of new data.[49,50] The systematic nature of study identification and inclusion criteria in the present analysis was designed to identify all available literature and provide the most robust estimates of intervention effect. However, the included studies came from a variety of hospital settings, in which the rate of patient safety events might vary. This is apparent in the clinical trial results presented by Mehta *et al.*, where colonoscopy and esophagogastroduodenoscopy were assessed independently due to differences in outcomes.[25] Analyses for particular settings were undertaken, but were then limited by reduced data availability. In total, this analysis represented 5,460 patients (control 2,755 and capnography 2,705) over 13 studies. Between trials, the number of patients enrolled varied between 132 and 986. Notably, of the six studies that identified rare outcomes (e.g. use of assisted ventilation), five enrolled >500 patients.

## CONCLUSIONS

The results of this comprehensive meta-analysis of clinical trials provide clear and consistent evidence of decreased respiratory compromise when capnography monitoring is used during procedural sedation and analgesia (PSA). Specifically, the analysis identified a statistically significant and clinically meaningful reduction in mild and severe oxygen desaturation, as well as in assisted ventilation. Large, well-designed, randomized controlled trials to provide direct links between use of capnography and reduction in patient harm may not be feasible. In turn, calls for this type of primary evidence may delay adoption of capnography monitoring during PSA as a valuable tool for early intervention and improved patient safety.

**Word Count** 5,233

## AUTHOR CONTRIBUTIONS

MM formulated the research question; RFP and RS devised the search strategy and data extraction protocol, which was critically reviewed and revised by MM, JRL and MMRFS; RFP and RS then conducted the literature searches, screening, data extraction, and meta-analysis, and co-wrote the manuscript; MM, JRL and MMRFS critically reviewed the manuscript and made substantive revisions prior to submission.

## DATA SHARING STATEMENT

All data used to derive the outcomes presented in the study are documented in the manuscript and supplementary materials. No additional data are therefore available.

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## TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## ETHICAL APPROVAL

No ethical approval was required for the study as all data were derived from published data; neither animal nor human subjects were enrolled as part of the present study.

## FUNDING AND STUDY SPONSOR ROLE

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## FINANCIAL AND COMPETING INTEREST DISCLOSURE

All authors have completed the Unified Competing Interest forms at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

- Michael Mestek is a full-time employee of Medtronic plc.

- Richard F Pollock is a full-time employee of Ossian Health Economics and Communications GmbH, which received research and consultancy fees from Medtronic plc. to conduct the literature review and meta-analysis and prepare the manuscript.
- Rhodri Saunders was a full-time employee of Ossian Health Economics and Communications GmbH at the time of performing the meta-analysis and is currently a director of Coreva Scientific GmbH & Co. KG.
- Michel MRF Struys's research group/department received grants and funding from The Medicines Company (USA), Masimo (USA), Fresenius (Germany), Acacia Design (The Netherlands), Medtronic (USA) and honoraria from The Medicines Company (USA), Masimo (USA), Fresenius (Germany), Baxter (USA), Medtronic (USA), Demed Medical (Belgium).
- Jenifer R Lightdale has served as a consultant for Medtronic and Norgine, and has received speaker honorarium from Mead-Johnson and Perrigo.

## TABLES AND FIGURES

**Table 1 Included studies reporting endpoints of interest**

| Study (reference) | Country | Trial dates | Modified Jadad † | Potential for bias | Hospital setting | Depth of sedation | Sedative | Monitoring staff | Oxygen at baseline | N (control, Cap) |
|---|---|---|---|---|---|---|---|---|---|---|
| Beitz 2012[28] | Germany | Feb-10, Jan-11 | 5.5 | High: 3 | Colonoscopy | "adequate" | Propofol | Not specified | 2 L/minute | 757 (374, 383) |
| Deitch 2010[26] | US | Nov-06, Feb-08 | 5.5 | Low: 0 | Emergency department | Moderate | Propofol | Not specified | 3 L/minute | 132 (64, 68) |
| Friedrich-Rust 2014[29] | Germany | Jun-12, May-13 | 6 | Low: 0 | Colonoscopy | Deep | Propofol+ | Anesthesiologist or sedation-trained nurse | 2 L/minute | 533 (266, 267) |
| Langhan 2015[31] | US | Sep-11, Jan-13 | 6 | Low: 0 | Pediatric emergency department | NA | Ketamine, midazolam | "Treating staff" | None | 154 (77, 77) |
| Lightdale 20066 | US | Dec-03, Nov-04 | 8 | Low: 0 | Endoscopy | Moderate | Fentanyl, midazolam | Independent observer | 2 L/minute | 163 (80, 83) |
| Qadeer 20095 | US | Jan-07, May-08 | 7.5 | Moderate: 1 | ERCP and EUS | NA | Midazolam+ | Independent observer | None | 247 (124, 123) |
| Slagelse 2013[32] | Denmark | Sep-10, Jan-11 | 6 | Low: 0 | Endoscopy | NA | Propofol | Sedation-trained nurse | 2-3 L/minute | 540 (277, 263) |
| van Loon 2014[27] | Netherlands | Apr-10, Jan-11 | 5 | Low: 0 | Gynecology | Deep | Propofol | Medical team providing sedation | None | 415 (209, 206) |
| Zongming 2014[30] | China | Nov-10, May-13 | 6 | Low: 0 | Abortion | Deep | Propofol | Anesthesiologist | 3 L/minute | 700 (359, 341) |
| Campbell 2016 | Canada | Apr-06, Apr-12 | 5 | Moderate: 2 | Emergency department | NA | Physician's choice | Paramedic acute care practioner | 98.7% received oxygen | 986 (501, 485) |
| Klare 2016[34] | Germany | Feb-10, Oct-11 | 5.5 | Moderate: 1 | ERCP | Deep | Midazolam and | Physician not | 2 L/minute | 238 (117, 121) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | propofol | performing procedure | | |
| Mehta 2016 (colon)[25] | US | Dec-13, Jan-15 | 8 | Low: 0 | Colonoscopy | Moderate | Fentanyl or meperidine, plus midazolam | Independent observer | None | 231 (114, 117) |
| Mehta 2016 (EGD)[25] | US | Dec-13, Jan-15 | 8 | Low: 0 | EGD | Moderate | Fentanyl or meperidine, plus midazolam | Independent observer | None | 209 (108, 101) |
| Riphaus 2016[33] | Germany | Jun-10, Nov-11 | 5.5 | High: 3 | EUS | "adequate" | Midazolam and propofol | Independent observer | 2 L/minute | 170 (87, 83) |

† Higher scores indicate higher quality studies. In the present analysis, a score of 6.0–8.0 was designated as high quality.
+, in combination with multiple other agents; BZP, benzodiazepine; Cap, Capnography (arm); EGD, Esophagogastroduodenoscopy; ERCP, Endoscopic retrograde cholangiopancreatography; EUS, Endoscopic ultrasonography

**Figure 1 Severe and mild desaturation are significantly reduced with capnography monitoring**

The risk ratios for the endpoints of mild desaturation (A) and severe desaturation (B) are presented. CI, Confidence interval; M-H, Mantel-Haenszel

**Figure 2 The need for assisted ventilation is reduced with capnography monitoring**

]The odds ratios for the assisted ventilation endpoint are presented for all studies (A), high quality studies (B), studies with low risk of bias (C), and studies with the end point specified as bag-mask ventilation (D). CI, Confidence interval; M-H, Mantel-Haenszel

**Table 2** **Sensitivity analyses around the primary analyses**

| Scenario | Desaturation, mild | Desaturation, severe | Apnea | Bradycardia | Hypotension | Assisted ventilation | Supplemental oxygen |
|---|---|---|---|---|---|---|---|
| **Base case (all studies)** | **0.77 [0.67, 0.89]** | **0.59 [0.43, 0.81]** | **1.17 [0.72, 1.89]** | **1.16 [0.88, 1.54]** | **1.02 [0.78, 1.33]** | 0.47 [0.23, 0.95] | **0.93 [0.75, 1.15]** |
| High quality studies | 0.75 [0.62, 0.92] | 0.57 [0.36, 0.92] | 0.89 [0.64, 1.23] | 1.26 [0.80, 1.99] | 0.97 [0.73, 1.30] | 0.56 [0.27, 1.20] | 0.98 [0.79, 1.23] |
| Moderate sedation | 0.80 [0.60, 1.07] | - | 0.99 [0.69, 1.42] | - | - | - | - |
| US only | 0.80 [0.64, 0.99] | 0.59 [0.26, 1.30] | 0.89 [0.64, 1.23] | - | 1.04 [0.57, 1.88] | - | - |
| Europe only | 0.77 [0.63, 0.96] | 0.61 [0.44, 0.84] | 2.83 [0.12, 67.30] | 1.18 [0.86, 1.61] | 0.90 [0.66, 1.24] | 0.49 [0.23, 1.03] | 0.91 [0.67, 1.25] |
| Studies with potential bias excluded | 0.78 [0.64, 0.95] | 0.65 [0.37, 1.14] | 0.99 [0.69, 1.42] | 1.26 [0.80, 1.99] | 0.92 [0.68, 1.25] | 0.56 [0.27, 1.20] | 1.16 [0.95, 1.41] |
| Studies in pediatrics excluded | 0.78 [0.67, 0.89] | 0.59 [0.43, 0.81] | 1.29 [0.75, 2.23] | 1.16 [0.88, 1.54] | 1.02 [0.78, 1.33] | 0.47 [0.23, 0.95] | 0.92 [0.74, 1.14] |
| Gender-specific studies excluded | 0.76 [0.66, 0.89] | 0.59 [0.41, 0.84] | 1.17 [0.72, 1.89] | 1.18 [0.84, 1.65] | 1.03 [0.75, 1.41] | 0.49 [0.23, 1.03] | 0.84 [0.68, 1.03] |
| Studies with mean age >30 years | 0.75 [0.65, 0.87] | 0.56 [0.41, 0.78] | 1.29 [0.75, 2.23] | 1.16 [0.88, 1.54] | 1.02 [0.78, 1.33] | 0.47 [0.23, 0.95] | 0.87 [0.71, 1.07] |

The reported treatment effect is the risk ratio (RR) [95% confidence interval], except for assisted ventialtion where the peto odds ratio (OR) [95% confidence interval] is used. CI, confidence interval; US, United States

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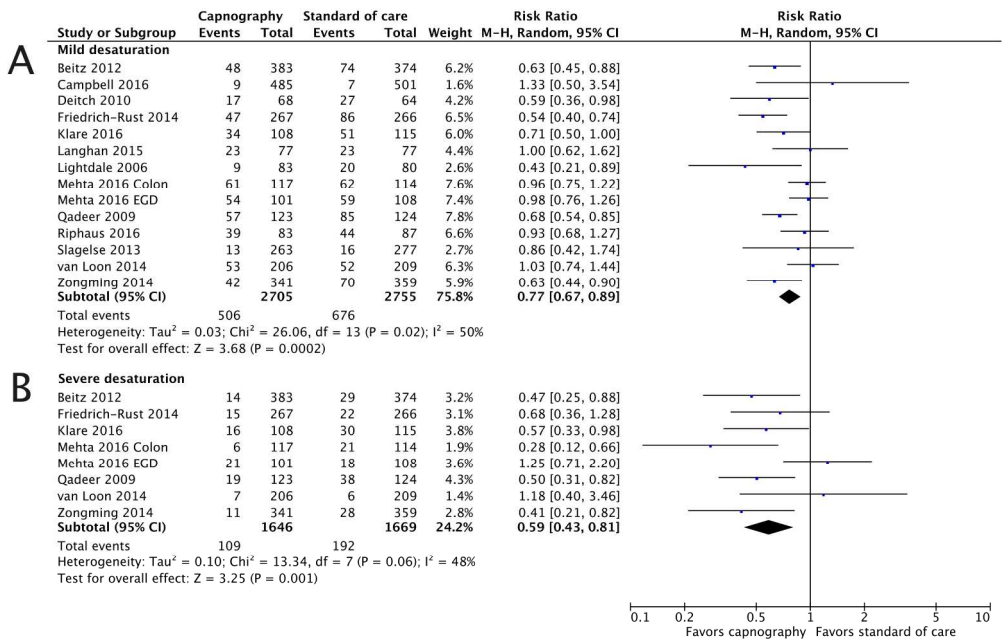
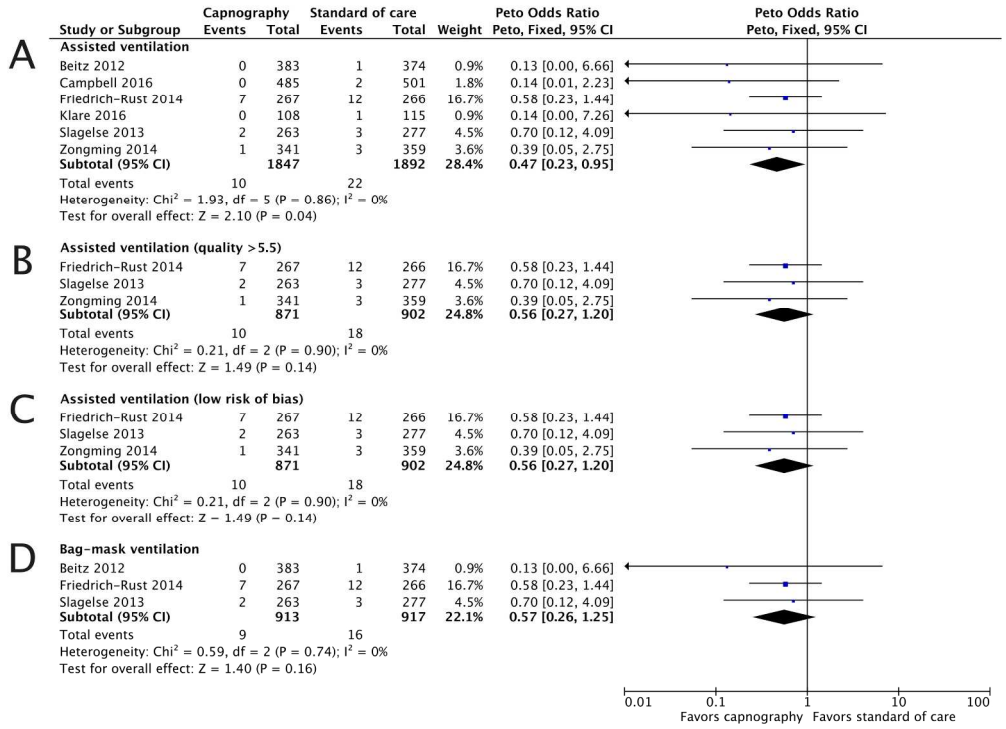



Severe and mild desaturation are significantly reduced with capnography monitoring
Figure 1
205x132mm (300 x 300 DPI)




The need for assisted ventilation is reduced with capnography monitoring
Figure 2
205x152mm (300 x 300 DPI)

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 22 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 22 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 23 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 19,24 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 16 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 17,24-27 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 17,24-27 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 18 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 18 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12-13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 14 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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