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ORIGINAL RESEARCH

The addition of capnography to standard monitoring reduces hypoxemic events during gastrointestinal endoscopic sedation: a systematic review and meta-analysis

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Background: The use of capnography monitoring devices has been shown to lower the rates of hypoxemia via early detection of respiratory depression, and facilitate more accurate titration of sedatives during procedures. The aim of the current meta-analysis was to compare the incidence of hypoxemia associated with standard monitoring alone during gastrointestinal endoscopy to that associated with standard monitoring with the addition of capnography.

Methods: The MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials scientific databases were searched to identify relevant studies. We performed a meta-analysis of randomized controlled trials undertaken up to January 2018 that met our predefined inclusion criteria. The study outcome measures were incidence of hypoxemia, severe hypoxemia, apnea, the use of assisted ventilation, the use of supplemental oxygen, and change in vital signs.

Results: We included nine trials assessing a total of 3,088 patients who underwent gastrointestinal procedural sedation. Meta-analysis of study outcome revealed that capnography significantly reduced the incidence of hypoxemia (odds ratio 0.61, 95% CI 0.49–0.77) and severe hypoxemia (odds ratio 0.53, 95% CI 0.35–0.81). However, there were no significant differences in other outcomes including incidence of apnea, assisted ventilation, supplemental oxygen, and changes in vital signs. Early procedure termination and patient satisfaction-related outcomes did not differ significantly in the capnography group and the standard monitoring group.

Conclusion: This study indicates that capnography monitoring is an important addition with regard to the detection of hypoxemia during gastrointestinal procedural sedation, and should be considered in routine monitoring during gastrointestinal endoscopy.

Keywords: endoscopy, additional monitoring, hypoxemia, apnea

Introduction

Sedation and analgesia are commonly used during gastrointestinal endoscopic procedures, and have been shown to increase the success rates of these procedures.[1] However, the use of sedative agents can result in respiratory depression, airway obstruction, hypoxemia, and adverse cardiopulmonary events.[2,3] Therefore, monitoring of vital signs including continuous pulse oximetry combined with a patient's breathing pattern is advocated in many national guidelines on sedation for gastrointestinal endoscopy.[4,5]

Capnography measures the carbon dioxide (CO_2) concentration throughout the respiratory cycle, which allows for real-time evaluation of a variety of respiratory factors including respiratory depression, apnea, and hypercapnia.[6] Hypoventilation can

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occur in the presence of normal arterial oxygen saturation as determined via pulse oximetry (SpO_2), and inadequate ventilation can precede hypoxemia by several minutes.[7,8] The use of a capnography monitoring device has been shown to lower the rates of hypoxemia via early detection of respiratory depression and facilitate more accurate titration of sedatives during procedures.[9]

The American Society of Anesthesiologists recommended that capnography monitoring should be considered for all patients receiving deep sedation.[5] However, there are insufficient data to demonstrate that improved clinical outcomes or care quality derive from the use of capnography in patients undergoing targeted moderate sedation for upper endoscopy and colonoscopy.[4,10,11] Furthermore, it has been suggested that capnography may lead to unnecessary procedure interruption, delay, or termination, contributing to inefficiency.[4] Thus, most guidelines for gastrointestinal sedation do not recommend routine use of capnography, but recommend it only in specific situations including high-risk patients, intended deep sedation, and long procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS).[4,11,12]

The aim of the current meta-analysis was to determine whether the addition of capnography to standard monitoring including pulse oximetry reduces hypoxemic events during gastrointestinal endoscopic sedation.

Methods

In this systematic review, determination of the criteria for the selection of studies, extraction of relevant data, assessment of study quality, and statistical analyses were conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement.[13]

Literature search

We conducted a systematic literature search using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials updated from 1979 to January 2018. The following Medical Subject Heading terms were used: "capnography", "hypoxia", "monitoring", "physiologic", "endoscopy", "endoscopic", "gastrointestinal", "gastroscopy", "gastroscopes", "colonoscopy", and "colonoscopes". All of these items were then explored to include secondary headings, and the reports considered were limited to those involving human subjects. Two investigators (SHK and YSC) independently reviewed all potentially relevant material to determine whether or not it met the inclusion criteria.

Inclusion and exclusion criteria and definitions

The inclusion criteria were as follows: 1) study population, patients undergoing gastrointestinal endoscopic sedation; 2) intervention, capnography monitoring; control, standard monitoring; 3) outcome measure, the incidence of oxygen desaturation; and 4) study design, prospective and randomized controlled trials (RCTs). Duplicate publications, review articles, case reports, studies without raw data available for retrieval, and studies only available as abstracts from conferences were excluded.

Evaluation criteria for endpoints

The primary endpoint of this study was the weighted summary OR of the incidence of hypoxemia (SpO_2 of $<90\%$ to $<95\%$) with a 95% CI. The secondary endpoints were 1) incidence of severe hypoxemia defined as SpO_2 of $<85\%$; 2) incidence of apnea; 3) early detection of apnea; 4) use of assisted ventilation; 5) use of supplemental oxygen; 6) bradycardia; 7) hypotension; 8) incidence of early procedure termination; 9) patient satisfaction; and 10) patient cooperation with regard to the endoscopic procedure.

Study selection and data extraction

After removing duplicate studies, two investigators (SHK and YSC) independently perused the titles and abstracts of all publications retrieved and assessed their eligibility for inclusion in the meta-analysis. If available, the full texts of selected studies were screened with reference to the inclusion and exclusion criteria. Selected full-text articles were critically appraised for relevance and validity. When any disagreement occurred, this was resolved by discussion, together with clinical expert consultation. The following information was extracted from the articles included: first author, year of publication, endoscopic procedure, monitoring intervention, patients' baseline characteristics, sedative agents, depth of sedation, duration of procedures, and primary and secondary outcomes. To avoid bias in the data extraction process, two investigators (SHK and YSC) independently evaluated each study quality and compared results with one another. In case of disagreement, the third investigator (EK) made a determination decision.

Assessment of methodological quality

The Cochrane Collaboration's risk of bias tool was used to assess the risk of bias in all included studies. The following items were assessed and recorded: random sequence generation (selection bias), allocation concealment (selection bias),

blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

GRADE assessment and summary of findings

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the quality of the evidence associated with specific outcomes (hypoxemia, severe hypoxemia, incidence of apnea, and detection of apnea) in our review and to construct a "summary of findings" table. The GRADE approach considers study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias.

Statistical analysis

All analyses were performed using Meta V.4.9–0 and Meta for V.2.0–0 in R packages (R language version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). We calculated the OR as a summary statistic with a 95% CI for dichotomous outcomes and the standardized mean difference with a 95% CI for continuous outcomes. Heterogeneity among the studies was measured using the I^2 statistic and the *P*-value was derived from the Cochran's *Q* test. Significant between-study heterogeneity was deemed to be present when there was an I^2 value of more than 50% or a Cochran's *Q* test *P*-value of <0.1.[14] The presence of publication bias was evaluated via Egger's test with a funnel plot.[15]

Results

Identification of studies

Nine studies derived from eight RCTs[6,7,9,16–20] in which a total of 3,088 patients who underwent gastrointestinal procedural sedation were enrolled were ultimately included in the final analysis (Figure 1). Overall, 1,542 patients were assigned to the capnography group, and the remaining 1,546 were assigned to the standard monitoring group.

Study characteristics and patient populations

Of the eight studies, four were performed in Germany, three were performed in the USA, and one was performed in Denmark. Endoscopic procedures included upper endoscopy, colonoscopy, EUS, ERCP, and other interventional procedures. One study, published by Mehta et al,[6] provided separate data on colonoscopy and esophagogastroduodenoscopy.

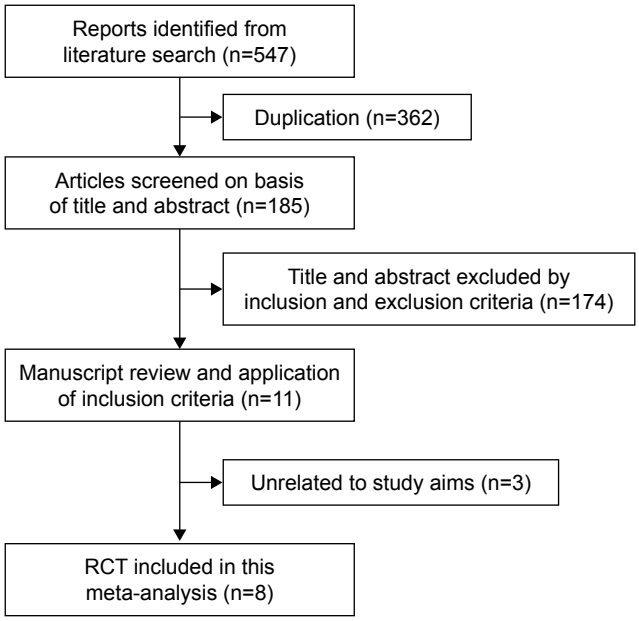

Figure 1 Flow diagram of study searching and selection process.
Abbreviation: RCT, randomized controlled trial.

Five studies used propofol as a sedative agent[7,9,18–20] and other studies used either fentanyl, midazolam, meperidine, or ketamine, or combination of these.[6,16,17] The main characteristics of the studies are presented in Table 1.

Apnea was defined as the absence of respiratory activity denoted by a flat line on the capnograph in 7 studies,[6,7,9,16,17,19,20] and hypoventilation was defined as a respiratory rate of less than or equal to 8/min in two studies.[6,19] In another two studies,[6,17] greater than a 75% reduction in the amplitude of the capnograph waveform compared with baseline for 5–10 seconds was defined as abnormal or disordered ventilation.

In five of the eight studies, the endoscopy team (physicians and nurses) was not blinded to the assignment of patients. Capnographic data were available for the capnography group, but not for the standard monitoring group. In the other three studies,[6,16,17] the endoscopy team was not aware of the capnographic findings, and capnographic data were only available to an independent observer. In these three studies, interventions were initiated in both groups based on capnography, albeit at different intervals (5–10 seconds for abnormal ventilation in the capnography group and >30 seconds for apnea in the standard monitoring group).

The studies included in this meta-analysis utilized four types of capnography. The Capnostream 20 (Oridion Medical, Needham, MA, USA) was used in four studies, and the other four studies used Capnostream 20 (Covidien, Mansfield, MA, USA), Philips M4 with Microstream CO_2 (Philips Medical

Table 1 The main characteristics of the studies included in the meta-analysis

Study (publication year)	Number (cap, control)	Population and procedures	Sedatives, depth of sedation	Duration of procedures (cap vs control, minute)	Definition of hypoxemia
Lightdale et al (2006)[16]	163 (83, 80)	ASA 1–2, children (0–19 years), endoscopy and colonoscopy	Fentanyl and midazolam, moderate	Endoscopy: 10 (0–24) vs 10 (4–25), colonoscopy: 39 (34–67) vs 40 (15–69)	SaO_2 <95% for 5 seconds
Qadeer et al (2009)[17]	247 (124, 123)	ASA 1–3, adults, ERCP or EUS	Midazolam in combination with meperidine or fentanyl, N/A	37.2 (16.1) vs 34.4 (12.5)	SaO_2 <90% for 15 seconds
Beitz et al (2012)[7]	757 (383, 374)	ASA 1–3, adults, colonoscopy	Propofol, adequate	35.9 (22.0) vs 33.8 (20.6)	Fall in SaO_2 ≥5% or <90%
Slagelse et al (2013)[18]	540 (263, 277)	ASA 1–3, adults, endoscopy or colonoscopy	Propofol, N/A	23.6 (12–30) vs 24 (13–31)	SaO_2 <92%
Friedrich-Rust et al (2014)[19]	533 (267, 266)	ASA 1–3, adults, colonoscopy alone or in combination with EGD	Propofol in combination with ketamine, N/A	38 (16) vs 38 (17)	SaO_2 <90% for 15 seconds
Klare et al (2016)[9]	238 (108, 115)	ASA 1–4, adults, ERCP	Propofol and midazolam, deep	38 (6–165) vs 38 (5–164)	SaO_2 <90%
Mehta et al (2016)[6]	209 (101, 108)	ASA 1–2, adults, endoscopy	Fentanyl or midazolam or meperidine, moderate	5.6 (2.6) vs 5.6 (2.6)	SaO_2 <90% for 10 seconds
Mehta et al (2016)[6]	231 (117, 114)	ASA 1–2, adults, colonoscopy	Fentanyl or midazolam or meperidine, moderate	17.3 (7.3) vs 17.4 (7.5)	SaO_2 <90% for 10 seconds
Riphaus et al (2017)[20]	170 (83, 87)	ASA 1–3, adults, interventional endoscopy (EUS or other interventional procedures)	Midazolam and propofol, adequate	25 vs 26	SaO_2 <90%

Notes: Duration of procedures are presented as mean (SD) or median (interquartile range).
Abbreviations: cap, capnography; ASA, American Society of Anesthesiologists; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; EGD, esophagogastroduodenoscopy; N/A, not applicable; SaO_2, oxygen saturation.

Systems, Andover, MA, USA; Oridion), Microcap (Oridion), and Philips MP 20 monitor, respectively.

Quality of the included studies

The risks of performances and outcome assessment biases were substantial due to lack of blinding. In five studies, neither the patients nor the endoscopy team was blinded, and there were no independent observers for the outcome assessment. The overall quality of the studies was moderate to low using the GRADE approach. We have included the risk of bias and a summary of findings in Tables S1 and S2, respectively.

Hypoxemia

All studies reported hypoxemia, with the definitions varying from SpO_2 of <90% to <95%. The study by Lightdale et al[16] was performed in pediatric patients, and the definition of hypoxemia was SpO_2 <95%, which was higher than that of the other studies. In another studies,[6,7,9,17–20] SpO_2 of <90%–<92% was the criterion for hypoxemia. Publication bias was assessed by Egger's test with a funnel tunnel plot (P=0.691).

The analysis revealed that capnography significantly reduced the incidence of hypoxemia (OR 0.61, 95% CI 0.49–0.77) (Figure 2). Six studies reported severe hypoxemia, defined as SpO_2 of <85%. The analysis showed that the addition of capnography to standard monitoring has benefit in reducing the incidence of severe hypoxemia (OR 0.53, 95% CI 0.35–0.81) (Figure 3).

Apnea

Apnea was assessed with capnography in four studies, and the incidence of apnea was comparable between the two groups (OR 0.74, 95% CI 0.39–1.43) (Figure 4). In these four studies, capnography was used to detect apnea in both groups. In three studies, the endoscopy team was unaware of the capnographic findings, and apnea was assessed by an independent observer. In the remaining study, the endoscopy team was not blinded to the capnographic findings, and the incidence of apnea was retrospectively analyzed in the standard monitoring group.

In another two studies, apnea was more frequently detected in the capnography group than in the control group (OR 44.76, CI 25.35–79.04) (Figure 5). In these two studies, capnography was only used in the capnography group and was not used to detect apnea in the standard monitoring group.

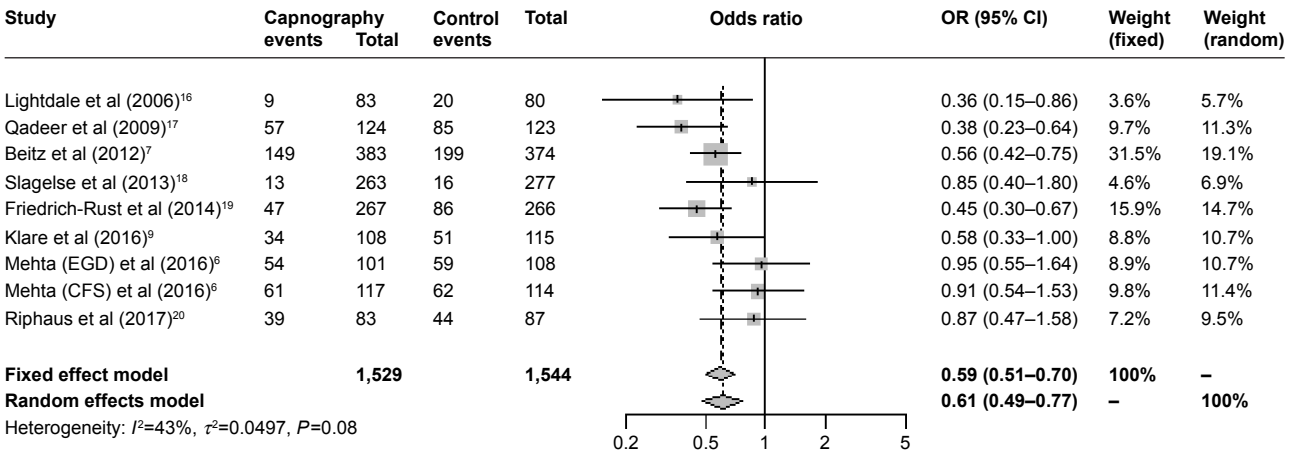

Figure 2 Forest plot showing the odds ratios and 95% CIs of each study for hypoxemia.
Abbreviations: EGD, esophagogastroduodenoscopy; CFS, colonoscopy.

Assisted ventilation and supplemental oxygen

Five studies reported on the use of assisted ventilation, and there was no evidence of heterogeneity (I^2=0%). The fixed effect model demonstrated that the need to provide assisted ventilation was comparable between the two groups (OR 0.56, 95% CI 0.25–1.22). The need to provide supplemental oxygen was reported in five studies, and analysis indicated that the provision of supplemental oxygen was comparable in the two groups (OR 0.74, 95% CI 0.52–1.03).

Other side effects

Seven studies reported bradycardia, with definitions varying from heart rates of <50 beats/min to <60 beats/min. Hypotension (systolic blood pressure varying from <100 mmHg to <80 mmHg) was reported in eight studies. The incidences of bradycardia (OR 1.18, 95% CI 0.84–1.65) and hypotension (OR 0.92, 95% CI 0.68–1.25) did not differ significantly between the two groups. Four studies reported the incidence of procedure termination secondary to concerns for patient safety, and there were no significant differences in early procedure termination (OR 4.96, 95% CI 0.24–104.39). Three studies reported patient satisfaction outcome and patient cooperation. Neither patient satisfaction (standard mean difference (SMD) −0.02, 95% CI −0.14 to 0.10) nor patient cooperation (SMD 0.00, 95% CI −0.12 to 0.11) differed significantly between the two groups.

Discussion

Recently, the use of sedatives has improved patient comfort and their acceptance of gastrointestinal endoscopy.[21] Interventional endoscopic procedures under endoscopic sedation via a sedative agent such as propofol are now used widely.[4] During endoscopic sedation, cardiorespiratory complications such as hypoxemia and apnea may occur, and require technical monitoring including pulse oximetry. However, this method only provides an indirect measure of respiratory function, and the detection of cardiorespiratory depression may potentially be delayed.[22]

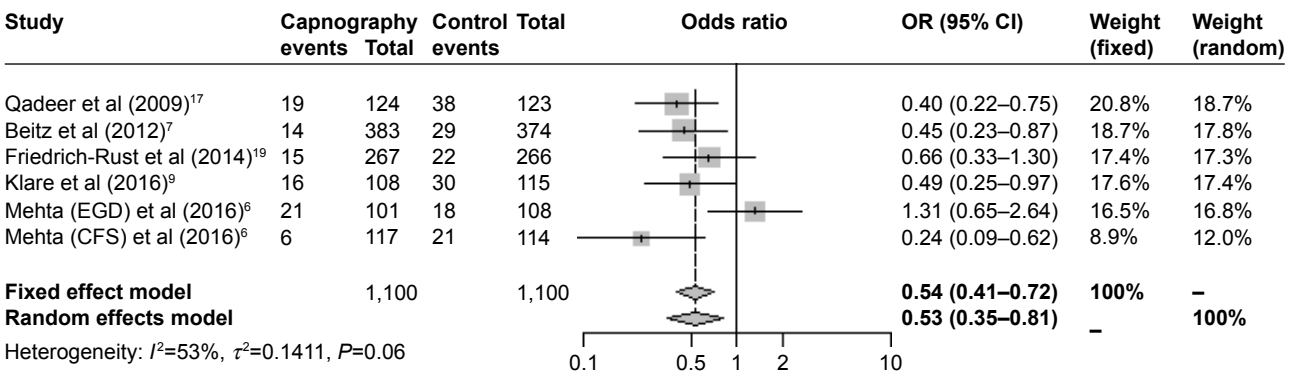

Figure 3 Forest plot showing the odds ratios and 95% CIs of each study for severe hypoxemia.
Abbreviations: EGD, esophagogastroduodenoscopy; CFS, colonoscopy.

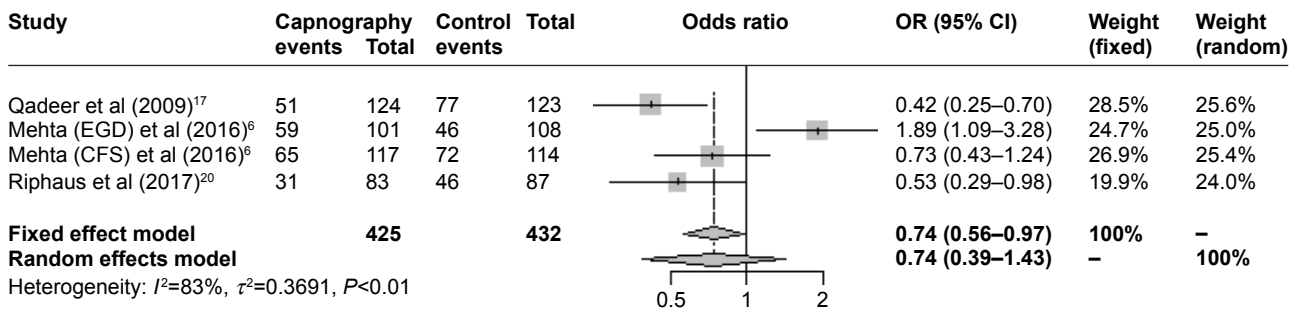

Figure 4 Forest plot showing the odds ratios and 95% CIs of each study for the incidence of apnea.
Abbreviations: EGD, esophagogastroduodenoscopy; CFS, colonoscopy.

Capnography facilitates continuous, real-time, non-invasive measurement of expiratory CO_2. Capnography monitoring entails the measurement of end-tidal CO_2 concentrations using an infrared sensor attached to a nasal cannula or face mask.[12] This facilitates the early detection of arterial oxygen desaturation via near real-time graphic assessment of respiratory activity. Many studies of surgical operations and non-surgical procedures have shown that the use of capnography monitoring is associated with a reduction in the incidence of hypoxemic events. Nevertheless, the use of capnography during gastrointestinal endoscopy is not an established recognized standard for monitoring respiratory function.

In a recent meta-analysis,[23] there was a lack of convincing evidence that the addition of capnography to standard monitoring in emergency departments reduced the rate of adverse events including hypoxemia. However, most of the procedures included in that analysis were orthopedic manipulation, abscess incision and drainage, or cardioversion, which differ from elective procedures. In another meta-analysis including gynecologic procedures, abortion, and emergency department procedures,[24,25] capnography reduced the rate of hypoxemia, which is consistent with the results of the current meta-analysis. Notably, there was no consensus on whether capnography could reduce the need for assisted ventilation in those two studies. Further, there was no previously published meta-analysis of the use of capnography during gastrointestinal endoscopic sedation.

In previous sedation guidelines for non-anesthesiologists, continuous monitoring via visual observation of breathing and its frequency was recommended, but capnography monitoring was not mandatory.[26] However, recent standards advocated by the American Society of Anesthesiologists suggest that the adequacy of ventilation should be evaluated via continuous capnography monitoring.[27]

The results of our meta-analysis show that capnography reduced the rate of hypoxemia during gastrointestinal sedation but was not significantly associated with incomplete endoscopic procedures or patient satisfaction. Many factors can influence respiratory depression, such as the degree and depth of sedation, the sedative agents used, the patient's baseline disease status, age, and the duration of the procedure during endoscopy. The nine studies assessed in the current investigation evaluated hypoxemia, and the median procedure times of four studies were >30 minutes. The duration of the procedure is an important risk factor for oxygen desaturation. Therefore, it is expected that the role of capnography will increase in future in conjunction with the ongoing development of interventional endoscopy procedures with long procedure times, and the widespread use of sedatives associated with those procedures.

The results of the current investigation showed that capnography has a beneficial effect by reducing the incidence of hypoxemia and severe hypoxemia during gastrointestinal endoscopic sedation. Because the target level of sedation was equal in both the standard monitoring and capnography

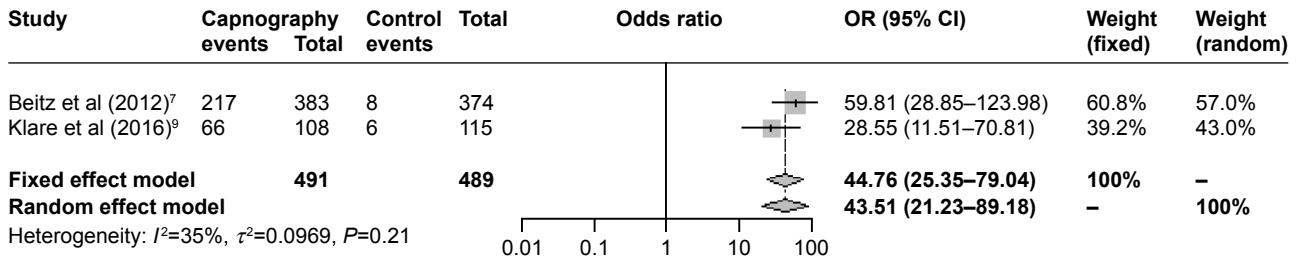

Figure 5 Forest plot showing the odds ratios and 95% CIs of each study for the detection of apnea.

groups, the incidence of apnea was not different between the two groups; however, in two studies evaluating the detection of apnea, there was no evidence of heterogeneity and the results showed that apnea was more often detected with the addition of capnography than it was in the standard monitoring group. Whereas most episodes of apnea might remain undetected using standard monitoring with visual assessment of the patient, the use of capnography can facilitate early interventions such as patient stimulation, withholding or reducing sedative medications, and using chin-lift or jaw-thrust maneuvers. Easier detection of apnea via capnography may explain the difference in the incidence of hypoxemia between the two groups, and these results demonstrate the value of adding capnography monitoring during sedation for gastrointestinal procedure.

The target level of sedation in the trials included in this study ranged from moderate to deep sedation. In moderate sedation, spontaneous ventilation is adequate and maintenance of airway patency does not require interventions.[5] However, it is not always possible to predict how a patient will respond to specific sedative and analgesic medications. Thus, the level of sedation could become deeper than initially intended. In this meta-analysis, the addition of capnography monitoring was effective in reducing hypoxemia, and it did not increase the rate of early procedure termination. Therefore, we suggest capnography monitoring should be considered for routine monitoring during gastrointestinal endoscopic procedures performed under moderate sedation in the future.

The present meta-analysis had several limitations that should be taken into account when interpreting the results. It included studies that varied with respect to the sedative agents and corresponding doses used. This may account for some of the heterogeneity in the results of the analysis. Second, because our analysis was based on only eight RCTs, we did not perform subgroup analysis based on the type of endoscopic procedure. Thus, it cannot be decisively concluded that diagnostic and therapeutic endoscopy have similar safety with regard to sedation. We also analyzed both upper endoscopy through the oral cavity and colonoscopy together. Further studies with larger numbers of patients are warranted to clarify the beneficial effects of capnography during gastrointestinal endoscopic sedation.

Conclusion

In the current meta-analysis, capnography monitoring was associated with reduced incidence of hypoxemia during gastrointestinal procedural sedation, and there was no evidence of an association with procedural interruption. Capnography monitoring should be considered in routine monitoring in the near future.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Risk of bias summary

Study (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Lightdale et al (2006)[16]	Low	Low	Low	Low	Low	Low
Qadeer et al (2009)[17]	Low	Low	Low	Low	Low	Low
Beitz et al (2012)[7]	Low	High	High	High	Low	Low
Slagelse et al (2013)[18]	Low	Low	High	High	Low	Low
Friedrich-Rust et al (2014)[19]	Low	Low	High	High	Low	Low
Klare et al (2016)[9]	Low	Low	High	High	Low	Low
Mehta et al (2016)[6]	Low	Low	Low	Low	Low	Low
Riphaus et al (2017)[20]	Low	Low	High	High	Low	Low

Table S2 GRADE approach

Date:
Question: Capnography monitoring compared to standard monitoring for gastrointestinal procedural sedation
Setting:
Bibliography:

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Capnography monitoring	standard monitoring	Relative (95% CI)	Absolute (95% CI)		
Hypoxemia (assessed with: oxygen saturation)												
9	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	463/1,529 (30.3%)	622/1,544 (40.3%)	**OR 0.61** (0.49–0.77)	**111 fewer per 1,000** (from 61 fewer to 154 fewer)	⊕⊕⊕◯ Moderate	Important
Severe hypoxemia (assessed with: oxygen saturation)												
6	Randomized trials	Serious[b]	Serious[c]	Not serious	Not serious	None	91/1,100 (8.3%)	158/1,100 (14.4%)	**OR 0.53** (0.35–0.81)	**62 fewer per 1,000** (from 24 fewer to 88 fewer)	⊕⊕◯◯ Low	Important
Incidence of apnea (assessed with: capnography)												
4	Randomized trials	Not serious	Serious[d]	Not serious	Not serious	None	206/425 (48.5%)	241/432 (55.8%)	**OR 0.74** (0.39–1.43)	**75 fewer per 1,000** (from 86 more to 228 fewer)	⊕⊕⊕◯ Moderate	Important
Detection of apnea (assessed with: capnography or visual inspection)												
2	Randomized trials	Serious[e]	Not serious	Not serious	Not serious	None	283/491 (57.6%)	14/489 (2.9%)	**OR 44.76** (25.35–79.04)	**540 more per 1,000** (from 399 more to 671 more)	⊕⊕⊕◯ Moderate	Important

Notes: [a]In five studies, endoscopy team was not blinded to assignment of patients because of organizational reasons. [b]In three studies, endoscopy team was not blinded to assignment of patients. [c]I2=75%. [d]I2=83%. [e]In two studies, endoscopy team was not blinded to assignment of patients.