A systematic review of capnography for sedation

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Short title: Capnography for sedation

Summary

We included six trials with 2524 participants. Capnography reduced hypoxaemic episodes, relative risk (95% CI) 0.71 (0.56-0.91), but the quality of evidence was poor due to high risks of performance bias and detection bias and substantial statistical heterogeneity. The reduction in hypoxaemic episodes was statistically homogeneous in the subgroup of three trials of 1823 adults sedated for colonoscopy, relative risk (95% CI) 0.59 (0.48-0.73), although the risks of performance and detection biases were high. There was no evidence that capnography affected other outcomes, including assisted ventilation, relative risk (95% CI) 0.58 (0.26-1.27), p = 0.17.

Keywords

Sedation, capnography

Introduction

Monitoring of depressed spontaneous ventilation is recommended during sedation [1, 2]. Respiratory function is usually evaluated by assessing airway patency, the rate and depth of breathing and oxygen saturation [2].

Ventilation can also be monitored with capnography. Hypoventilation, due to airway obstruction or central respiratory depression, is likely to precede hypoxaemia in the sedated patient and can be detected by changes in the capnographic waveform [3]. Capnography could trigger earlier clinical intervention that prevents hypoxaemia. Fewer episodes of hypoxaemia would indicate that capnography might be safer than standard monitoring [4]. However, premature stimulation of the patient in response to hypoventilation may be counterproductive and result in inadequate sedation [5]. Furthermore, numerous clinically irrelevant physiological alarms can lead to 'alarm fatigue', which has been associated with deaths resulting from delayed responses to clinical deterioration [6, 7]

Capnography therefore should be evaluated rigorously to determine the harm and benefit it causes sedated patients [8]. Our primary objective of was to determine whether capnography reduces hypoxaemia in comparison with standard monitoring for sedated patients. Our secondary objective was to determine whether capnography affected clinical interventions.

Methods

We included parallel and cross-over randomised controlled trials of adults or children sedated for procedures in hospital, with vs without capnography, published in any language [9]. Our primary outcome was hypoxaemia, as defined by the study authors. The secondary outcomes were: increased supplemental oxygen; airway intervention; doses of sedatives and analgesics; sedative antagonism; the rate of incomplete procedures due to inadequate sedation; the rates of adverse events.

We searched to June 2015: CENTRAL; MEDLINE; CINAHL; ClinicalTrials.gov; and the World Health Organization International Clinical Trials Registry Platform (online Supplementary File). Two authors (AC and CD) independently screened titles, abstracts and full text articles, extracted data and assessed risks of bias using the Cochrane tool [10]. Disagreements were resolved through discussion. We categorised statistical heterogeneity as substantial if the I^2 statistic exceeded 50%, for which we planned subgroup trial analyses: adults vs children (ages for children were as defined by the study authors); sedation by anaesthetist vs not; routine vs ad hoc supplemental oxygen; propofol vs benzodiazepine vs benzodiazepine and opioid vs ketamine vs dexmedetomidine vs other; respiratory depression protocol vs none; and procedures that were similar in duration and invasiveness.

We calculated relative risks (95% CI) for dichotomous outcomes and mean differences (95% CI) for continuous outcomes. We used fixed-effect and random-effects models for meta-analysis with RevMan (computer program version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) [10] and standard GRADE evidence assessment of outcomes [11].

Results

We included six trials with 2524 participants (Fig. 1 and Table 1) having: colonoscopies [12-14]; emergency department procedures [15, 16]; and gynaecological procedures [17]. Three trials implemented protocols to titrate sedation to capnography measurements [12,13,17]. Five trials used propofol to sedate adults [12-15, 17] and one study used midazolam or ketamine to sedate children [16]: all participants were ASA physical status < 4. The risks of performance and assessment biases were substantial due to lack of blinding (Fig. 2).

Capnography reduced hypoxaemia (Fig. 3). The pooled evidence from the six trials was of poor quality due to risks of bias and statistical heterogeneity. The pooled estimate from three trials of adults given supplemental oxygen during sedation with propofol for colonoscopy was homogeneous: capnography reduced hypoxaemia from 207/1000 to 120/1000. The rate of hypoxaemia was unaffected by capnography in the other three trials. There were no consistent effects of capnography on secondary outcomes: the relative risk (95% CI) for assisted ventilation was 0.58 (0.26-1.27), p = 0.17.

Discussion

Capnography reduced the rate of hypoxaemia during sedation but did not alter other outcomes. The effect appeared to be restricted to three similar trials that sedated participants during colonoscopy with propofol whilst supplying supplemental oxygen.

A previous meta-analysis of observational studies reported that respiratory depression was 18 times more likely to be detected with capnography than pulse oximetry alone [3]. We expected that capnography would cause changes in clinical management, such as oxygen flow and airway interventions. It is unclear how capnography caused less hypoxaemia as we did not identify any differences in the clinical management of participants enrolled in these trials.

The end tidal capnographic concentration may be different to the arterial partial pressure of carbon dioxide, the levels of which are inversely related to arterial oxygen. Transcutaneous carbon dioxide monitoring detects arterial hypercarbia more accurately than end-tidal carbon dioxide during sedation and might supplement capnography in future trials [19]. Future research might confirm whether or not a benefit of capnography applies more generally to sedated patients and what mechanisms mediate any effects. Such research should precede recommendations that capnography becomes mandatory for sedated patients. The Academy of Medical Royal Colleges Standard and Guidance report on Safe Sedation Practice for Healthcare Procedures noted that capnography is not mandatory but recommended that capnography be implemented in the long term [18].

Pooled data from three trials that reported severe respiratory depression were underpowered to detect a reduction from the control rate of 16/987 [12-14]. We excluded two trials relevant to this issue because the control group also used capnography: an independent observer signalled clinicians if alveolar hypoventilation was detected by capnography at different time intervals in both intervention and control groups [20, 21]. Both of these trials identified statistically significant reductions in oxygen desaturation. The trials we included that did report an effect of capnography did not all use explicit protocols to determine what actions should be taken in response to respiratory depression.

In our protocol, we defined hypoxaemia as an arterial partial pressure of oxygen < 60 mmHg or S_PO_2 < 90%, which is different to the definitions used by the trials we subsequently included in our systematic review. Nevertheless, we pooled data as we assumed that the definition of hypoxaemia used by the authors of each trial was appropriate for the context in which the study was performed. There were insufficient trials to construct funnel plots and to

investigate small study effects, including publication bias. We tried to minimise biased inclusion of published studies by searching multiple databases and registries [23].

The evidence for an effect of capnography was limited to adults sedated with propofol: we do not know whether these results would be replicated for children or patients sedated with other drugs, such as benzodiazepines and opioids, which are being investigated in one ongoing trial [22]. Further research should also determine whether capnography reduces hypoxaemia in sedated patients receiving supplemental oxygen flow in excess of three litres, which, in the authors' experience, is typical for sedated patients who can tolerate an oxygen mask. Researchers should concentrate on blinding interventions to limit bias and increase confidence in the effects of capnography for sedated patients.

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References

1. Gross J, Farmington C, Bailey P, et al. Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 2002; **96:** 1004-17.
2. Australia and New Zealand College of Anaesthetists. Guidelines on Sedation and/or Analgesia for Diagnostic and Interventional Medical or Surgical Procedures. Secondary Guidelines on Sedation and/or Analgesia for Diagnostic and Interventional Medical or Surgical Procedures 2014. http://www.anzca.edu.au/resources/professional-documents/professional-standards/pdfs/PS9.pdf.
3. Waugh JB, Epps CA, Khodneva YA. Capnography enhances surveillance of respiratory events during procedural sedation: a meta-analysis. *Journal of Clinical Anesthesia* 2011; **23:** 189-96.
4. Robbertze R, Posner KL, Domino KB. Closed claims review of anesthesia for procedures outside the operating room. *Current Opinion in Anesthesiology* 2006; **19:** 436-42.
5. Hung A, Tsao RW, Bukoye B, Barnett SR, Leffler D. 1055 Capnographic Monitoring of Moderate Sedation During Colonoscopy Does Not Improve Safety or Patient Satisfaction: a Prospective Cohort Study. *Gastrointestinal Endoscopy* 2015; **81:** AB193.
6. Sendelbach S, Funk M. Alarm fatigue: a patient safety concern. *AACN advanced critical care* 2013; **24:** 378-86.
7. Wallis L. Alarm fatigue linked to patient's death. *AJN The American Journal of Nursing* 2010; **110:** 16.
8. Sheahan C, Mathews D. Monitoring and delivery of sedation. *British Journal of Anaesthesia* 2014; **113:** ii37-ii47.
9. Conway A, Douglas C, Sutherland J. Capnography monitoring during procedural sedation and analgesia: a systematic review protocol. *Systematic Reviews* 2015; **4:** 92.
10. Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions Version 5.1.0 [Updated March 2011]. The Cochrane Collaboration. 2011. Available from www.cochrane-handbook.org
11. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* 2008; **336:** 924-6.

12. Slagelse C, Vilmann P, Hornslet P, Jørgensen HL, Horsted TI. The role of capnography in endoscopy patients undergoing nurse-administered propofol sedation: a randomized study. *Scandinavian Journal Of Gastroenterology* 2013; **48:** 1222-30.
13. Beitz A, Riphaus A, Meining A, et al. Capnographic monitoring reduces the incidence of arterial oxygen desaturation and hypoxemia during propofol sedation for colonoscopy: a randomized, controlled study (ColoCap Study). *The American Journal of Gastroenterology* 2012; **107:** 1205-12.
14. Friedrich-Rust M, Welte M, Welte C, et al. Capnographic monitoring of propofol-based sedation during colonoscopy. *Endoscopy* 2014; **46:** 236-44.
15. Deitch K, Miner J, Chudnofsky CR, Dominici P, Latta D. Does end tidal CO 2 monitoring during emergency department procedural sedation and analgesia with propofol decrease the incidence of hypoxic events? A randomized, controlled trial. *Annals of emergency medicine* 2010; **55:** 258-64.
16. Langhan ML, Shabanova V, Li F-Y, Bernstein SL, Shapiro ED. A randomized controlled trial of capnography during sedation in a pediatric emergency setting. *The American Journal Of Emergency Medicine* 2015; **33:** 25-30.
17. van Loon K, van Rheineck Leyssius AT, van Zaane B, Denteneer M, Kalkman CJ. Capnography during deep sedation with propofol by nonanesthesiologists: a randomized controlled trial. *Anesthesia & Analgesia* 2014; **119:** 49-55.
18. Academy of Medical Royal Colleges. Safe Sedation Practice for Healthcare Procedures. London, UK, 2013. Available from www.aomrc.org.uk
19. De Oliveira G, Ahmad S, Fitzgerald P, McCarthy R. Detection of hypoventilation during deep sedation in patients undergoing ambulatory gynaecological hysteroscopy: a comparison between transcutaneous and nasal end-tidal carbon dioxide measurements. *British Journal of Anaesthesia* 2010; **104:** 774-8.
20. Lightdale JR, Goldmann DA, Feldman HA, Newburg AR, DiNardo JA, Fox VL. Microstream capnography improves patient monitoring during moderate sedation: a randomized, controlled trial. *Pediatrics* 2006; **117:** e1170-e8.
21. Qadeer MA, Vargo JJ, Dumot JA, et al. Capnographic monitoring of respiratory activity improves safety of sedation for endoscopic cholangiopancreatography and ultrasonography. *Gastroenterology* 2009; **136:** 1568-76.
22. The Cleveland Clinic. Does the Use of Capnography in Routine EGD and Colonoscopy Targeting Moderate Sedation With a Benzodiazepine and Opioid Improve Safety? In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of

Medicine (US). [cited 2015 Sep 11]. Available from: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01994785

23. Glasziou P, Irwig L, Bain C and Colditz G. Systematic reviews in health care: a practical guide. Cambridge: Cambridge University Press; 2002.

Table 1 Characteristics of six trials of capnography during sedation

Study	Number	Population	Interventions	Comparison	Outcomes
Slagelse et al. 2013 [12]	540	Adult endoscopy; nurse-administered propofol; 2-3 $l.min^{-1}$ O_2 Excluded: OSA; propofol allergy; BMI > 35 $kg.m^{-2}$; Mallampati 4; acute bleeding; ileus; gastric retention; FEV_1 < 30%	Nurse-monitored $ETCO_2$ > 7 kPa or < 2 kPa or loss of capnographic curve for > one min, breathing < $8.min^{-1}$	No capnography	S_PO_2 < 92%; oral or nasal airway; abandoned procedure; assisted ventilation
Beitz et al. 2012 [13]	757	Adult colonoscopy; nurse-administered propofol; 2 $l.min^{-1}$ O_2	Independently observed for: no CO_2 or $ETCO_2$ < 50% baseline	Independently observed, no capnography	S_PO_2 < 90%; changed O_2 flow; propofol dose; assisted ventilation
Friedrich-Rust et al. 2013 [14]	533	Adult colonoscopy and gastroscopy; propofol administered by nurse or anaesthetist or other doctor; 2 $l.min^{-1}$ O_2	Acoustic and visual alarm for no CO_2 > 10 s	No capnography	S_PO_2 < 90% for > 10 s; changed O_2 flow; propofol dose; intubation; death; disability; cardiac arrest
Deitch et al. 2009 [15]	150	Adult emergency department procedures; propofol; 3 $l.min^{-1}$ O_2 Excluded: COPD; O_2 supplementation; respiratory distress; haemodynamic instability; pregnancy; propofol allergy	Clinician-monitored capnography	Clinician-monitored, no capnography	S_PO_2 < 93% for > 15 s; propofol dose; clinical intervention
Langhan et al. 2015 [16]	154	Children 1-20 years emergency department procedures; midazolam and ketamine Excluded: intubated; O_2 supplementation; asthma; diabetic ketoacidosis; dehydration; trauma; crying for > 20% of the procedure; intolerance of nasal cannulae	Alarms for $ETCO_2$ < 30 mmHg and > 50 mmHg.	No capnography	S_PO_2 < 95%; clinical intervention; changed O_2 flow; airway intervention; assisted ventilation; sedation reversed
Van Loon et al. 2014 [17]	427	Adult minor gynaecological procedures; nurse-administered propofol	$ETCO_2 \geq 6.7$ kPa, no plateau or apnoea >10 s, breathing < $9.min^{-1}$ or > $30\ .min^{-1}$	No capnography	S_PO_2 < 91%; changed O_2 flow; propofol dose; abandoned procedure; airway intervention

$ETCO_2$, end tidal carbon dioxide partial pressure; S_pO_2, pulse oxyhaemoglobin saturation

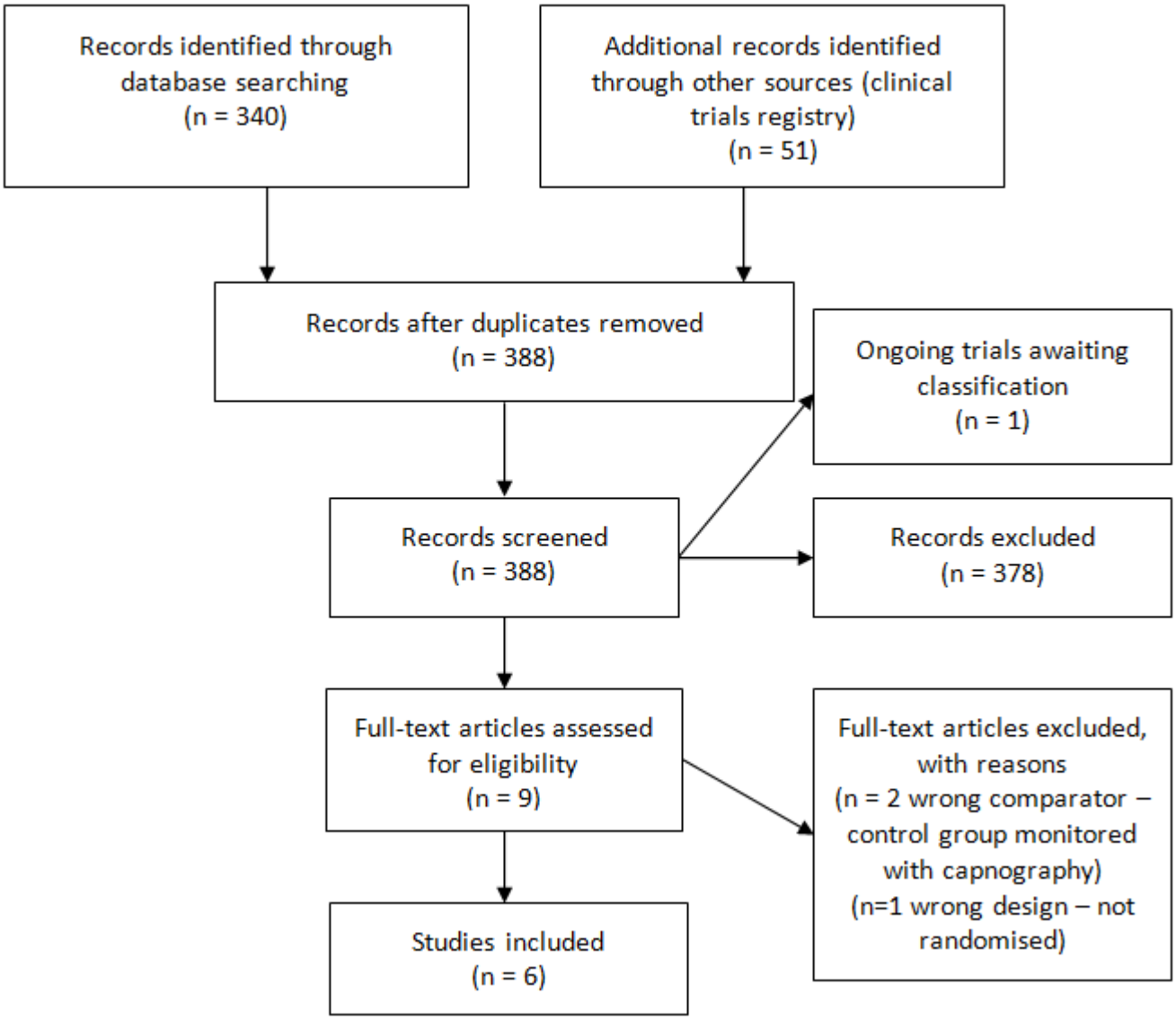

Figure 1 PRISMA flow diagram of trial selection

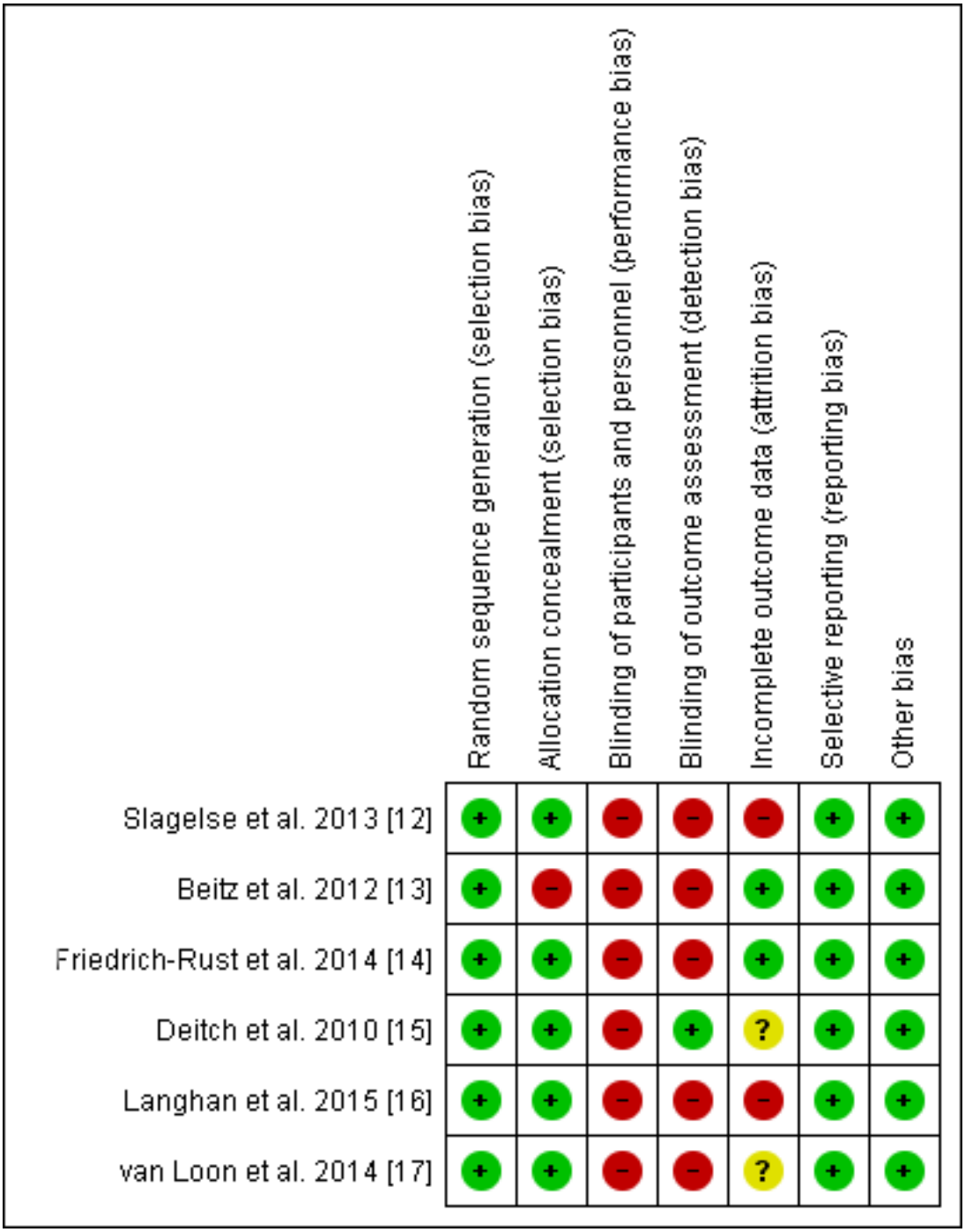

Figure 2 Risks of bias summary: low (green); unclear (yellow); and high (red)

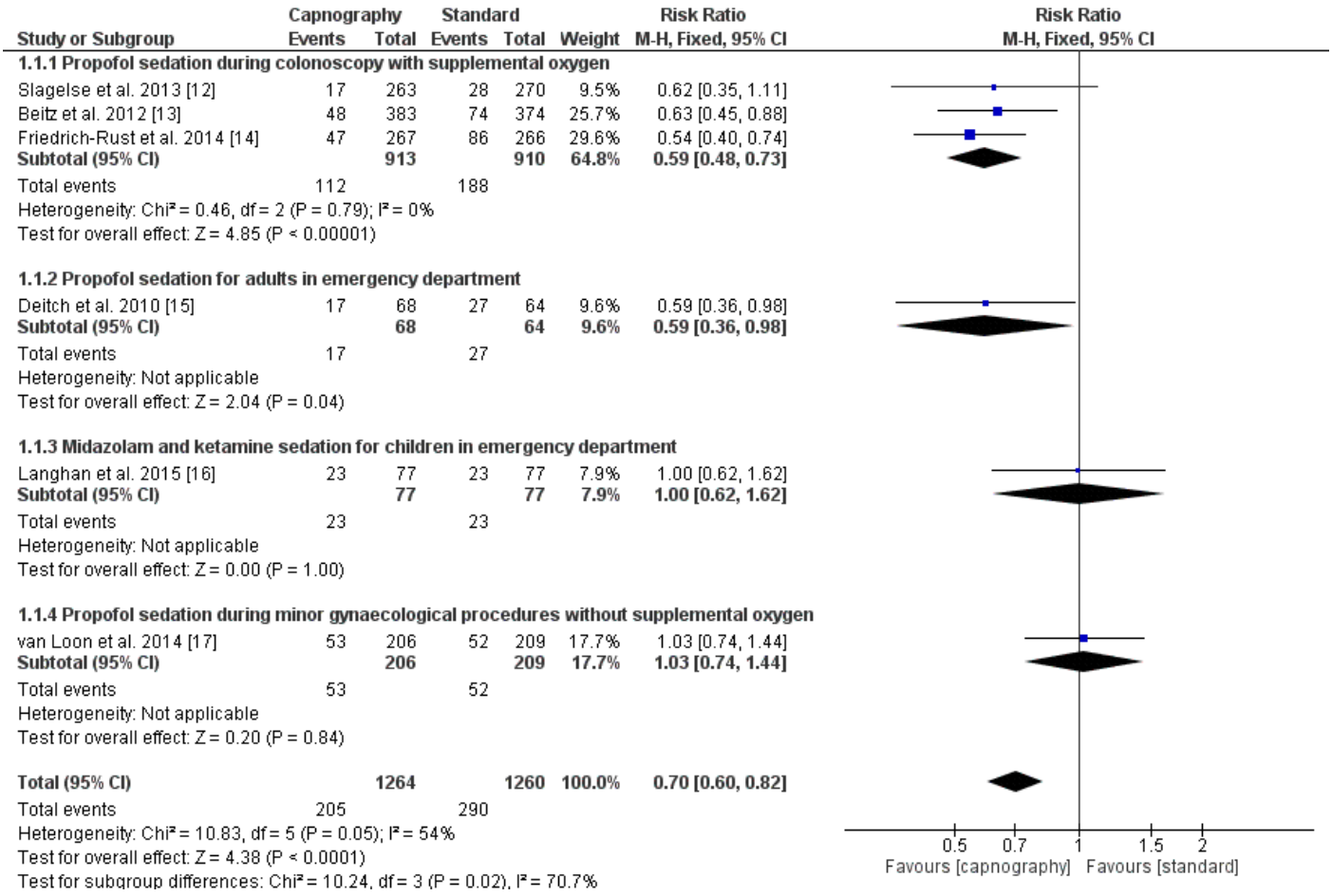

Figure 3 Forest plot of rates of hypoxaemia