**Supplemental Digital Contents (SDC)**

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|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Database** | **Search platform** | **Search terms and Boolean operators** | **Article types** | **Search fields** | **Other limitations** |
| Cochrane Library | Wiley® online library | (‘patient-controlled’ OR ‘patient-maintained’) AND ‘sedation’ AND ‘propofol’ | Trials, Reviews | All text | None |
| Medline | PubMed | No limitations | All fields |
| Embase | Ovid®, Expert Search | No limitations | Not specified |

**Table B.** Summary of included trials.

### Alhashemi 2006

|  |  |
| --- | --- |
| **Procedure** | Extracorporeal shock wave lithotripsy |
| **Patients** | Number = 64  Males = 83%  Mean (SD) age PCS/CCS = 41(10)/45(11) years  Mean (SD) weight PCS/CCS = 81(15)/75(14) kg  Mean (SD) height PCS/CCS = 163(8)/163(5) cm  ASA physical status = I-II |
| **PCS** | Bolus 0.3 mg kg-1 (lock-out time 3 min) |
| **CCS** | Clinician = anesthesiologist  Loading dose 200 μg kg-1 min-1 for 10 min  Continuous infusion 0.05-0.15 mg-1 kg-1 min as required |
| **Recommended depth of sedation in CCS group** | Patient comfort and lack of movement |
| **Concomitant drugs and anesthesia** | Preoperative midazolam 10 μg kg-1  Preoperative fentanyl 1 μg kg-1  Fentanyl 0.5 μg kg-1 h-1  Fentanyl 50 μg as required |
| **Inclusion criteria** | 18 - 80 years old  Renal or ureteric calculi  Scheduled for extracorporeal shock wave lithotripsy |
| **Exclusion criteria** | History of chronic analgesic or sedative use  History of alcohol abuse  Language barrier or mental disorder impeding use of pump  Allergy to study drugs |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 92% on O2 2 L min-1  Intervention for adverse event |
| **PCS device** | IVAC PCAM TM (Alaris Medical Sytems, Hampshire, UK) |
| **Sponsor** | Departmental funds |

### Bell 2010

|  |  |
| --- | --- |
| **Procedure** | Various |
| **Patients** | Number = 166  Males = 54%  Median (IQR) age PCS/CCS = 39 (25 -59.8)/39 (22.8 – 57.3) years  Mean weight PCS/CCS = 75/74.5 kg  ASA physical status = I-III |
| **PCS** | Loading dose 0.75 mg kg-1 (0.5 mg kg-1 if > 65 yrs)  Bolus 20 mg (lock-out time 1 min) |
| **CCS** | Clinician = emergency physician  Bolus as required |
| **Recommended depth of sedation in CCS group** | Clinician’s own judgment |
| **Concomitant drugs and anesthesia** | Fentanyl or morphine as required |
| **Inclusion criteria** | Patients requiring mild to moderate sedation for procedure in the emergency room |
| **Exclusion criteria** | History of propofol intolerance  History of allergy to eggs or soybeans  Communication barrier or cognitive or physical disability impeding use of pump  Pregnancy  Age < 16 years |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 92% on O2 2 L min-1  Systolic blood pressure < 80 mmHg  Heart rate < 60 min-1  Obstructed airway  Total propofol dose (mg)  Deepest sedation on Observer’s Assessment of Alertness/Sedation scale  Physician satisfaction  Patient satisfation |
| **PCS device** | Master PCA pumpTM (Fresenius Kabi, Homberg, Germany) |
| **Sponsor** | Queensland Emergency Medicine Research Foundation |

### Cork 1995

|  |  |
| --- | --- |
| **Procedure** | Various |
| **Patients** | Number = 43  Males = 37%  Mean (SEM) age PCS/CCS = 44(4)/46(3) years  Mean (SD) weight PCS/CCS = 77(4)/81(4) kg  Mean (SD) height PCS/CCS = 166(2)/171(2) cm  ASA physical status = I-II |
| **PCS** | Loading dose 0.5 mg kg-1  Continuous infusion 0.05 mg kg-1 min-1  Bolus 30 mg (lock-out time 3 min) |
| **CCS** | Clinician = anesthesiologist  Loading dose 0.5 mg kg-1  Continuous infusion 0.05 mg kg-1 min-1  Bolus 30 mg (lock-out time 3 min) |
| **Recommended depth of sedation in CCS group** | Mild slowing and thickening of speech |
| **Concomitant drugs and anesthesia** | Preoperative fentanyl 1 μg kg-1  Local anesthesia, spinal anesthesia, intravenous regional anesthesia |
| **Inclusion criteria** | Patients scheduled for ambulatory procedures |
| **Exclusion criteria** | History of allergy to propofol or soybeans  Intellectual impairment  Disability impeding use of pump  ASA physical status > II |
| **Endpoints used in meta-analysis** | Intervention for adverse event  SpO2 < 90%  Cumulative propofol dose (mg) |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 90%  Intervention for adverse event |
| **PCS device** | Bard Ambulatory PCATM (CR Bard Inc, North Reading, Massachusetts, USA) |
| **Sponsor** | None reported |

### Crepeau 2005

|  |  |
| --- | --- |
| **Procedure** | Colonoscopy |
| **Patients** | Number = 72  Males = 66%  Mean age PCS/CCS = 56.8/58.4 years  Mean BMI PCS/CCS = 26.3/26.1  ASA physical status = I-III |
| **PCS** | Bolus 20 mg (lock-out time 1 min) |
| **CCS** | Clinician = anesthesiologist  Target-controlled infusion as required |
| **Recommended depth of sedation in CCS group** | Patient comfort and adequate sedation |
| **Concomitant drugs and anesthesia** | Opiates as required |
| **Inclusion criteria** | Patients 18 – 80 years old, scheduled for colonoscopy |
| **Exclusion criteria** | ASA physical status > III  Contraindication for propofol  Pregnancy  Concomitant indication for upper endoscopy  Strong suspicion of colonic cancer  Emergency procedure  Therapeutic procedure and/or indication for coloration  Severe psychiatric disease  Inability to use pump, read French or sign consent |
| **Primary endpoint(s)** | Patient satisfaction |
| **Endpoints used in meta-analysis** | Heart rate decrease > 10%  Maximal depth of sedation on Wilson Sedation Scale |
| **PCS device** | AlarisTM |
| **Sponsor** | None reported |

### Heuss 2004

|  |  |
| --- | --- |
| **Procedure** | Various |
| **Patients** | Number = 74  Males = 58%  Mean (SD) age PCS/CCS = 64(15)/64(15) years  Mean (SD) weight PCS/CCS = 74(18)/74(17) kg  Mean (SD) height PCS/CCS = 168.8(9.6)/170.4(8.4) cm  ASA physical status = I-III |
| **PCS** | Loading dose 20 mg  Bolus 10 mg (lock-out time 1 min) |
| **CCS** | Clinician = gastroenterologist  Loading dose 20 mg  Bolus 10 mg (lock-out time 20 sec) |
| **Recommended depth of sedation in CCS group** | Response to simple verbal commands with or without tactile stimulation |
| **Concomitant drugs and anesthesia** | Pethidine 0.4 mg kg-1 |
| **Inclusion criteria** | Elective endoscopy as a sole endoscopic procedure  Wish to be sedated  ASA physical status I – III  Age above 18 years  Informed consent of sedation with propofol and use of data for research |
| **Exclusion criteria** | Propofol intolerance, including sensitivity to eggs or soybeans  Intravenous drug abuse  Physical handicap impeding use of pump  Communication barrier impeding understanding of PCS and informed consent |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 90% on O2 2 L min-1  Intervention for adverse event  Total propofol dose (mg)  Patient satisfaction (visual analogue scale 0-10 cm)  Endoscopist’s judgment (visual analogue scale 0-10 cm) |
| **PCS device** | Graseby 3’300TM (Graseby Medical, Watford, UK) |
| **Sponsor** | AstraZeneca |

### Mandel 2010

|  |  |
| --- | --- |
| **Procedure** | Colonoscopy |
| **Patients** | Number = 50  Males = 60%  Mean (SD) age PCS/CCS = 58(9.5)/59.1(10.8) years  Mean (SD) weight PCS/CCS = 84.7(22.6)/76.8(18.9) kg  Mean (SD) height PCS/CCS = 174.1(9.8)/169.7(8.9) cm |
| **PCS** | Loading dose 4 mg as required until moderate sedation level  Bolus 3 mg (lock-out time 6 sec) |
| **CCS** | Clinician = anesthesiologist  Loading dose 4 mg as required until moderate sedation level  Bolus 3 mg (loading dose 6 sec) |
| **Recommended depth of sedation in CCS group** | Response to the loudly spoken question, “Are you sleepy?”. In addition, clinicians were assisted by a software designed to predict sedation depth according to propofol dose and stimulation intensity |
| **Concomitant drugs and anesthesia** | Remifentanil 3 μg/bolus (lock-out time 6 sec) |
| **Inclusion criteria** | Scheduled colonoscopy  18 – 90 years old |
| **Exclusion criteria** | Woman of child-bearing potential  Allergy to propofol or remifentanil  Inability to understand use of pump  Significant cardiac or pulmonary comorbidity |
| **Primary endpoint(s)** | Respiratory rate  Bispectral index |
| **Endpoints used in meta-analysis** | SpO2 < 90% for > 30 sec on FiO2 100%  Intervention for adverse event  Total propofol dose (mg) |
| **PCS device** | Graseby 3’300TM (Marcal Medical Inc; Millersville, Maryland, USA) |
| **Sponsor** | Bioniche Pharma; Abott Laboratories; Merck |

### Maroof 1993

|  |  |
| --- | --- |
| **Procedure** | Extracorporeal shock wave lithotripsy |
| **Patients** | Number = 32  Males = 90%  Mean (SD) age PCS/CCS = 40.7(8.3)/43.8(13.5) years  Mean (SD) weight PCS/CCS = 71(12.4)/72.2(18.1) kg  ASA physical status = I-II |
| **PCS** | Loading dose 0.5 mg kg-1  Bolus 0.33 mg kg-1 (lock-out time 3 min) |
| **CCS** | Clinician = anesthesiologist  Loading dose 0.5 mg kg-1  Bolus 0.33 mg kg-1 as required |
| **Recommended depth of sedation in CCS group** | Optimal sedation and analgesia |
| **Concomitant drugs and anesthesia** | Preoperative pethidine 1 mg kg-1  Preoperative promethazine 0.25 mg kg-1  Fentanyl 0.165 μg/bolus (lock-out time 3 min) |
| **Inclusion criteria** | Scheduled extracorporeal shock wave lithotripsy for renal or ureteric stones  18 – 90 years old |
| **Exclusion criteria** | Cardiorespiratory disease |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 95% on O2 4 L min-1  Bradycardia  Intervention for adverse event  Total propofol dose (mg)  Patient satisfaction (numerical scale 1-10)  Patient cooperation (numerical scale 0-10) |
| **PCS device** | Bard PCA InfusorTM |
| **Sponsor** | None reported |

### Mazanikov 2013

|  |  |
| --- | --- |
| **Procedure** | Endoscopic retrograde cholangiopancreatography |
| **Patients** | Number = 79  Males = 62%  Mean (SD) age PCS/CCS= 47(11)/46(13) years  Mean BMI PCS/CCS = 23.4/23.4  ASA physical status = I-III |
| **PCS** | Bolus 10 mg (no lock-out time) |
| **CCS** | Clinician = anesthesiologist  Target-controlled infusion 2 μg ml-1 ± 0.5 μg ml-1 |
| **Recommended depth of sedation in CCS group** | Response to tactile stimulation |
| **Concomitant drugs and anesthesia** | Alfentanil 0.5 mg as required |
| **Inclusion criteria** | Not specified |
| **Exclusion criteria** | Allergy to propofol, alfentanil or lidocaine  ASA physical status > III  Chronic alcoholism or substance abuse  Inability to cooperate  Patient refusal |
| **Primary endpoint(s)** | Propofol consumption |
| **Endpoints used in meta-analysis** | SpO2 < 90% on O2 4 L min-1  Systolic blood pressure < 90 mmHg  Intervention for adverse events  Total propofol dose (mg)  Oversedation (absence of response to non-painful tactile stimulation) |
| **PCS device** | Syramed μSP6000TM (Arcomed AG, Regensdorf, Switzerland) |
| **Sponsor** | Departmental funding |

### Nilsson 2015

|  |  |
| --- | --- |
| **Procedure** | Endoscopic retrograde cholangiopancreatography |
| **Patients** | Number = 181  Males = 60%  Mean (SD) age PCS/CCS = 67 (15)/69 (15) years  Mean (SD) weight PCS/CCS = 75 (14)/74 (14) kg  Mean (SD) BMI PCS/CCS = 25.3 (4.7)/27.1 (5.1)  ASA physical status = I-III |
| **PCS** | Loading dose 6-10 boluses  Bolus 5 mg (no lock-out time) |
| **CCS** | Clinician = anesthesia nurse  Loading dose 5-10mg kg-1  Continuous infusion 2-8 mg kg-1 h-1 |
| **Recommended depth of sedation in CCS group** | Patient response after calling name loudly and/or repeatedly |
| **Concomitant drugs and anesthesia** | Topical anesthesia of throat |
| **Inclusion criteria** | Not specified |
| **Exclusion criteria** | Allergy to propofol  Pregnancy  ASA physical status > III  Use of Spy-GlassTM equipment during ERCP  History of dementia, confusion or other communication problem |
| **Primary endpoint(s)** | Risk of insufficient sedation |
| **Endpoints used in meta-analysis** | SpO2 < 90% on O2 3 L min-1  Systolic blood pressure < 90 mmHg on two consecutive measurements  Heart rate < 40 beats per minute  Need of interventions by clinician  Total propofol dose  Patient’s overall comfort (visual analogue scale 0 – 100mm)  Risk of deep sedation (absence of response to loud commands) |
| **PCS device** | T34LTM, PCA, CME Ltd., Liechtenstein |
| **Sponsor** | None reported |

### Singh 2005

|  |  |
| --- | --- |
| **Procedure** | Various |
| **Patients** | Number = 100  Mean (SD) age PCS/CCS = 35.1(12.1)/36.4(9.8) years  Mean (SD) weight PCS/CCS = 51.4(7.4)/51.1(8.9) kg  ASA physical status = I-II |
| **PCS** | Loading dose 0.5 mg kg-1  Bolus 30 mg (lock-out time 3 min) |
| **CCS** | Clinician = anesthesiologist  Loading dose 0.5 mg kg-1  Continuous infusion as required |
| **Recommended depth of sedation in CCS group** | Eyes closed, response to verbal command |
| **Concomitant drugs and anesthesia** | Spinal anesthesia |
| **Inclusion criteria** | Elective surgery under spinal anesthesia  ASA I-II |
| **Exclusion criteria** | Anticipated difficult airway  Significant respiratory or cardiovascular disease  Unable to understand PCS |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 90%  Systolic blood pressure < 80 mmHg  Intervention for adverse event  Oversedation (absence of response to loud commands) |
| **PCS device** | Not reported |
| **Sponsor** | None reported |

### Stonell 2006

|  |  |
| --- | --- |
| **Procedure** | Colonoscopy |
| **Patients** | Number = 40  Males = 80%  Mean (SD) age PCS/CCS = 46(13)/47(13) years  Mean (SD) weight PCS/CCS = 79(14)/84(29) kg  ASA physical status = I-III |
| **PCS** | Target-controlled infusion 0.8 μg ml-1 ± 0.1 μg ml-1 |
| **CCS** | Clinician = anesthesiologist  Bolus as required |
| **Recommended depth of sedation in CCS group** | Response to calling a patient’s name loudly |
| **Concomitant drugs and anesthesia** | Preoperative fentanyl 1 μg kg-1 |
| **Inclusion criteria** | Not specified |
| **Exclusion criteria** | ASA > III  Language barrier  Cognitive deficit, intellectual disability  Inability to use PCS handset  Inpatient |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 94% on O2 4 L min-1  Systolic blood pressure < 90 mmHg  Airway obstruction  Total propofol dose (mg)  Over-sedation (unresponsive to loud command or mild prodding)  Patient satisfaction (visual analogue scale 0-100 mm)  Operator satisfaction (visual analogue scale 0-100 mm) |
| **PCS device** | Asena GH MkIIITM (Alaris Medical Systems, Basingstoke, UK) |
| **Sponsor** | None reported |

### Wahlen 2008

|  |  |
| --- | --- |
| **Procedure** | Orthopedics |
| **Patients** | Number = 100  Males = 48%  Mean (SD) age PCS/CCS = 66(11)/68(10) years  Mean (SD) BMI PCS/CCS = 28.9(4.8)/30.3(4.3)  ASA physical status = I-III |
| **PCS** | Bolus 0.25 mg kg-1 (no lock-out time) |
| **CCS** | Clinician = anesthesiologist  Loading dose 0.25 mg kg-1  Continuous infusion as required |
| **Recommended depth of sedation in CCS group** | Eyes closed, responsive |
| **Concomitant drugs and anesthesia** | Spinal anesthesia |
| **Inclusion criteria** | Not specified |
| **Exclusion criteria** | Language barrier  Mental disorder  Allergy to propofol  Acute renal failure  Chronic renal insufficiency (≥ stage 2)  Acute hepatic failure (Child–Pugh classification ≥ A)  Pregnancy  Hiatus hernia  Acid reflux  Drug and alcohol dependence |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | SpO2 < 90% on O2 3 L min-1  Oversedation  Patient satisfaction (numerical scale 0-10) |
| **PCS device** | IVAC P5000TM, Alaris Medical Systems, Baesweiler, Germany |
| **Sponsor** | Departmental funding |

### Yun 2008

|  |  |
| --- | --- |
| **Procedure** | Cataract |
| **Patients** | Number = 102  Males = 38%  Mean (SD) age PCS/CCS = 69(9.6)/66.9(7.4) years  Mean (SD) weight PCS/CCS = 58.9(10.8)/63.3(10.1) kg  Mean (SD) height PCS/CCS = 159.3(8.7)/159.2(10) cm  ASA physical status = I-III |
| **PCS** | Loading dose 10 mg  Bolus 10 mg (lock-out time 1 min) |
| **CCS** | Clinician = nurse anesthetist  Bolus 10 mg (lock-out time 1 min) |
| **Recommended depth of sedation in CCS group** | At clinician’s discretion |
| **Concomitant drugs and anesthesia** | Local anesthesia |
| **Inclusion criteria** | Not specified |
| **Exclusion criteria** | Clinical evidence of heart failure  Severe pulmonary disease  Sedative medication during the month prior to operation  Difficulty with language or communication  Poor vision in the non-operated eye |
| **Primary endpoint(s)** | Not specified |
| **Endpoints used in meta-analysis** | Blood pressure decrease > 30%  Intervention for adverse event  Total propofol dose (mg)  Oversedation (unarousable to non-painful tactile stimulation)  Patient comfort (numerical scale 0-10)  Operator satisfaction (numerical scale 0-10) |
| **PCS device** | Auto Med 3’200TM (Ace-medical, Co., Seoul, Korea) |
| **Sponsor** | None reported |

ASA = American Society of Anesthesiologists; BMI = body mass index; CCS = clinician-controlled sedation; FiO2 = inspiratory fraction of oxygen; IQR = interquartile range; PCS = patient-controlled sedation; SD = standard deviation; SEM = standard error of the mean; SpO2 = peripheral capillary oxygen saturation.

**Table C.** Unpublished data included in meta-analysis.

|  |  |  |
| --- | --- | --- |
| **Trials** | **Unpublished data included in meta-analysis** | **Matching published data** |
| Bell | Means and SDs for total propofol dose | Box –Whisker-Plots |
| Mandel | SDs for total propofol dose and patient satisfaction | Means |
| Nilsson | Event rates for oxygen desaturation, arterial hypotension, bradycardia and rescue interventions for adverse events for patients in PCS group | Event rates for randomized and non-randomized patients combined in PCS group |
| Stonell | Number of patients with at least one event of oxygen desaturation, arterial hypotension, need for rescue interventions for adverse events and oversedation | Mean number of events per patient |

SD = standard deviation; PCS = patient-controlled sedation.

**Table D.** Risk of bias assessment.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Random sequence generation | Allocation concealment | Performance bias | Detection bias | Attrition bias | Reporting bias | Other biases |
| Alhashemi | - | ? | - | - | - | ? | - |
| Bell | - | - | + | + | ? | ? | - |
| Cork | - | ? | + | + | ? | ? | - |
| Crepeau | - | - | + | + | - | ? | - |
| Heuss | - | ? | + | + | ? | ? | - |
| Mandel | - | - | + | + | - | ? | - |
| Maroof | ? | + | + | + | ? | ? | - |
| Mazanikov | ? | ? | + | + | + | ? | + |
| Nilsson | - | ? | + | + | - | + | - |
| Singh | - | ? | + | + | - | ? | - |
| Stonell | - | - | - | - | - | ? | - |
| Wahlen | - | ? | + | - | - | ? | - |
| Yun | - | ? | + | + | - | ? | - |

“-“ = low risk of bias, “?” = unclear risk of bias, “+” = high risk of bias

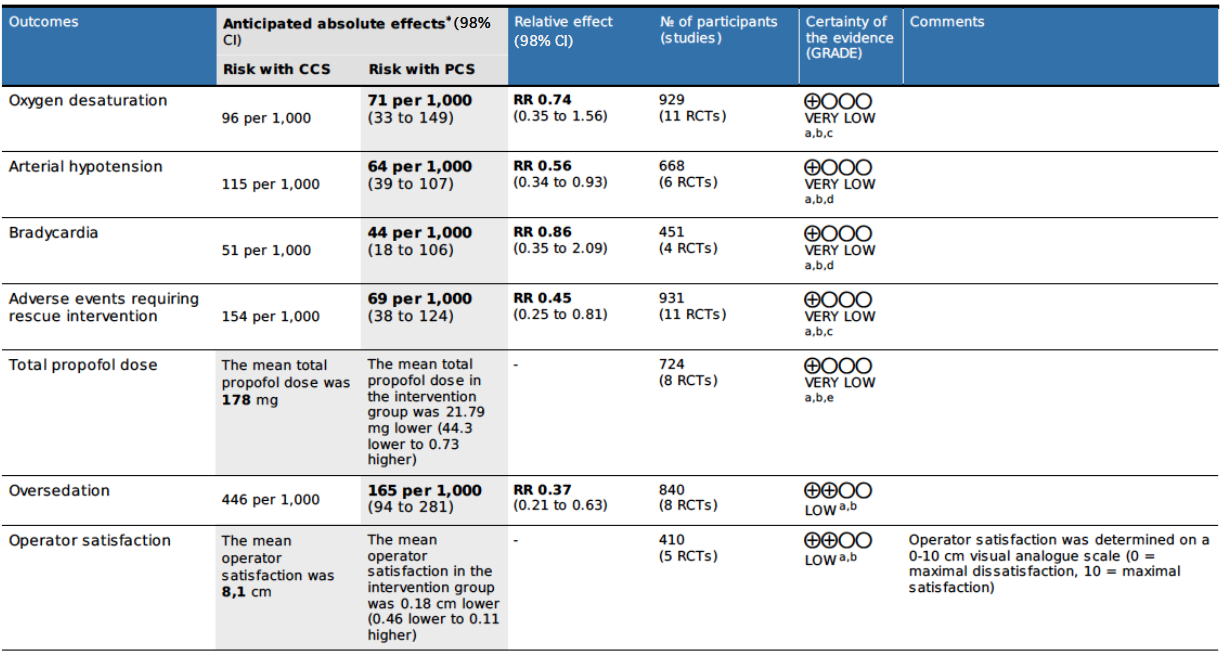
**Table E.** Literature search in trial registries (to October 2017).

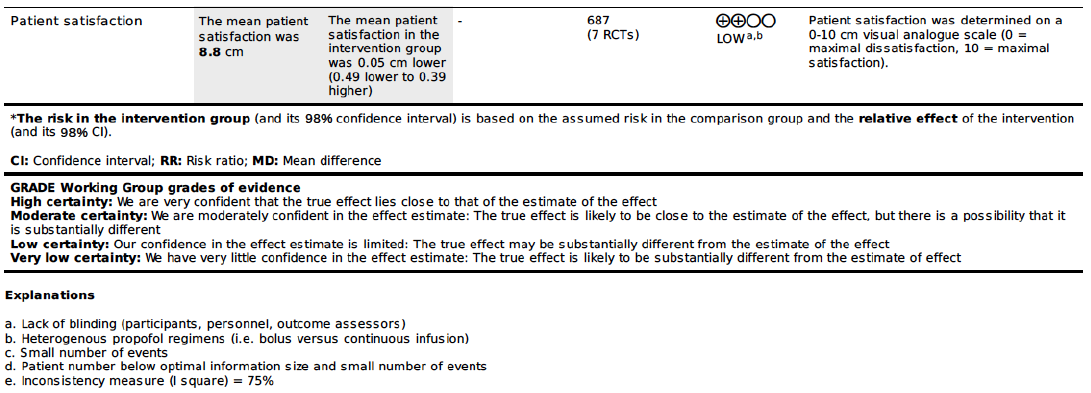
Search terms and Boolean operator: ‘patient-controlled’ AND ‘sedation’ AND ‘propofol’

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trial register** | **No. of identified trials** | **No. of withdrawn trials prior to enrollment** | **No. of published trials not included in systematic review** | **No. of published trials included in systematic review** |
| clinicaltrials.gova | 17 | 0 | 0 | 36,8,9 |
| EU clinical trials registerb | 8 | 0 | 0 | 18 |
| Japan Primary Registries Networkc | 0 | 0 | 0 | 0 |
| International Standard Randomised Controlled Trial Numberd | 0 | 0 | 0 | 0 |
| Australian New Zealand Clinical Trials Registrye | 0 | 0 | 0 | 0 |

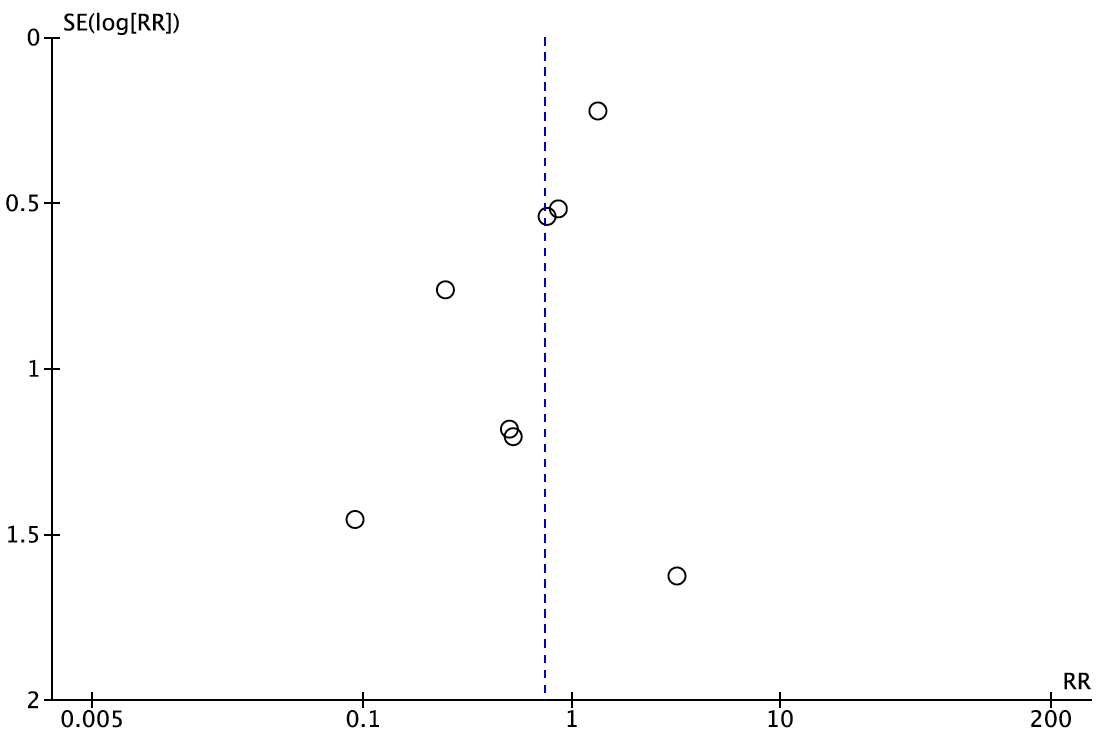
a https://clinicaltrials.gov; b https://www.clinicaltrialsregister.eu; c http://rctportal.niph.go.jp/en;

d https://www.isrctn.com; e http://www.anzctr.org.au.

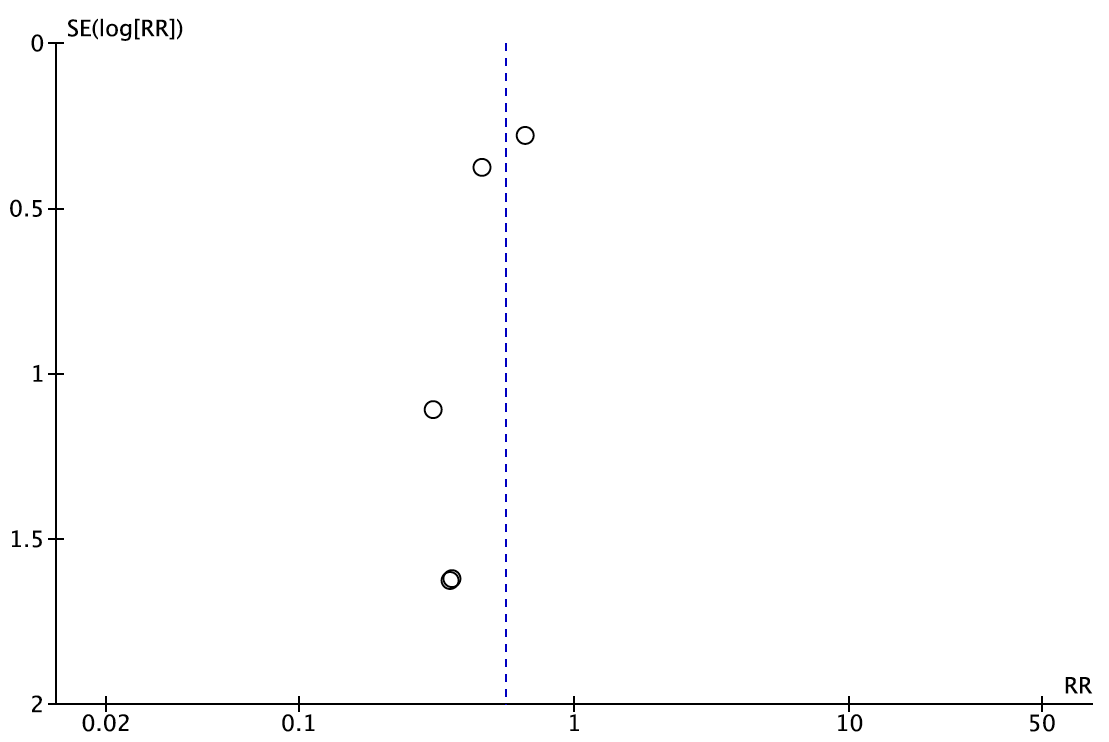
**Table F.** GRADE summary of findings.



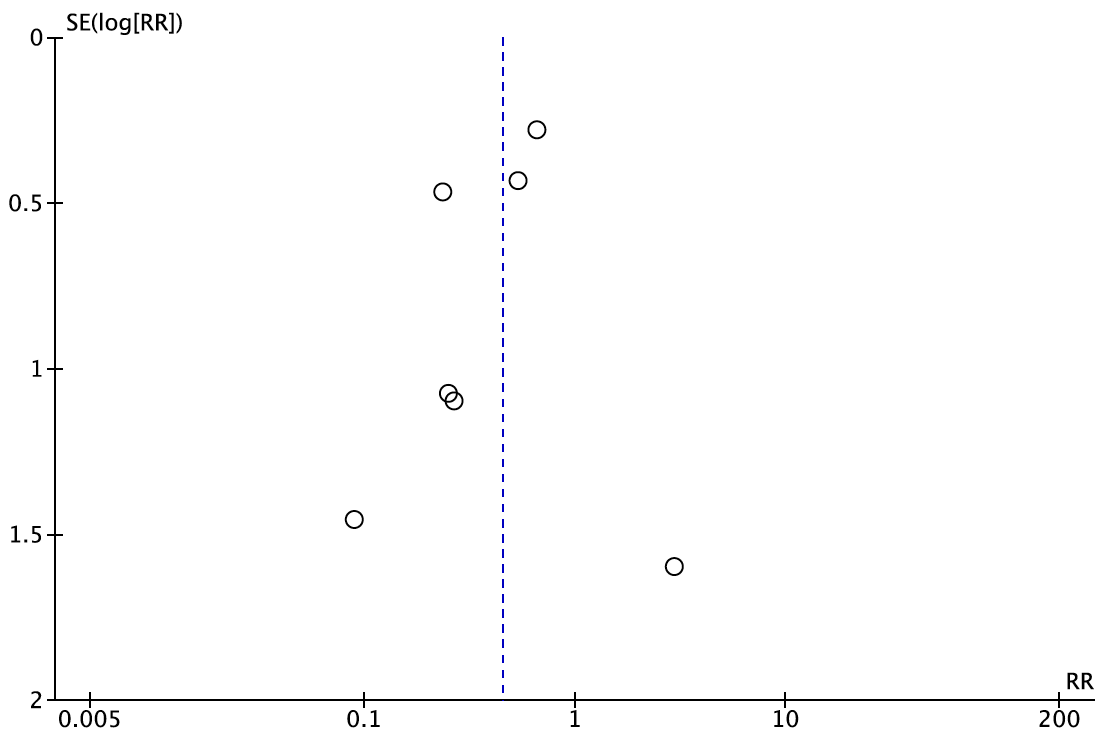
**Figure A.** Funnel plot for risk of oxygen desaturation. Risk ratio; SE = standard error**.** Dotted line indicates overall RR for oxygen desaturation (RR = 0.74)



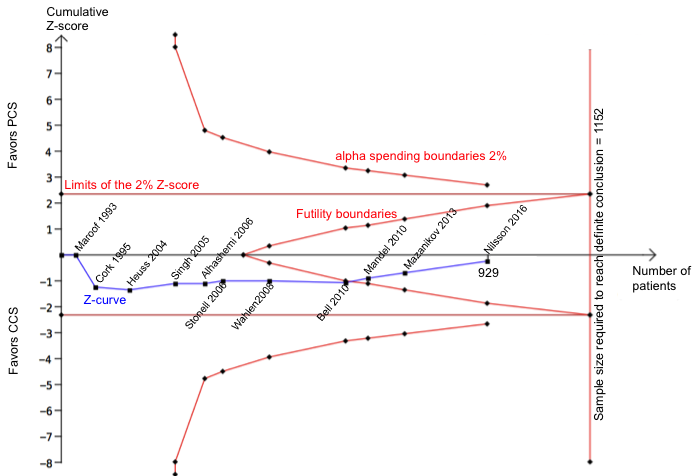
**Figure B.** Funnel plot for risk of arterial hypotension. RR = risk ratio; SE = standard error**.** Dotted line indicates overall RR for arterial hypotension (RR = 0.56)



**Figure C.** Funnel plot for risk of rescue intervention for adverse events. RR = risk ratio; SE = standard error**.** Dotted line indicates overall RR for rescue intervention for adverse events (RR = 0.45).

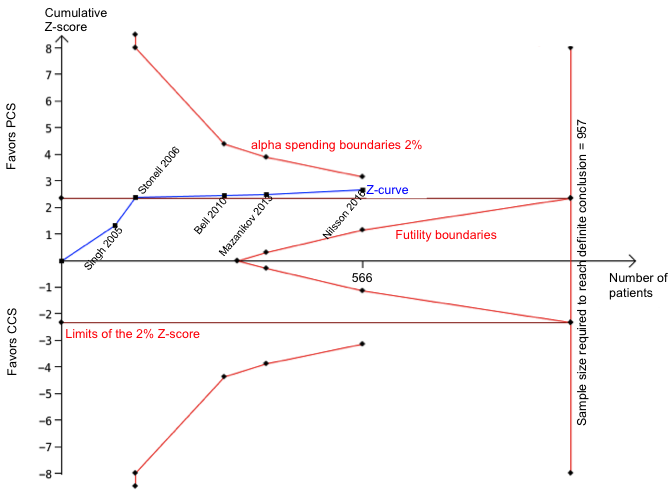


**Figure D.** Trial sequential analysis for risk of oxygen desaturation. PCS = patient-controlled sedation; CCS = clinician-controlled sedation.



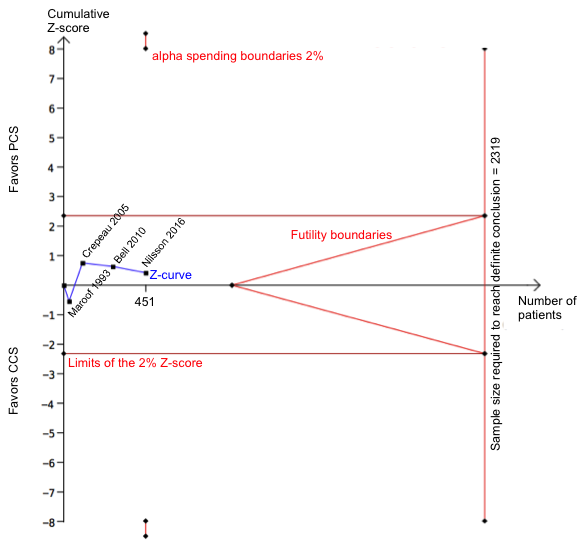
Trial sequential analysis suggests that the required sample size needed to reach a definitive conclusion regarding the capacity of PCS to reduce oxygen desaturation by 50% compared with CCS is 1152 patients, and is therefore not yet reached with 929 patients. However, the cumulative Z-line (in blue) has crossed the line for futility since the Mandel et al. trial in 2010,6 suggesting that future trials are unlikely to change our conclusion.

**Figure E.** Trial sequential analysis for risk of arterial hypotension. PCS = patient-controlled sedation; CCS = clinician-controlled sedation.



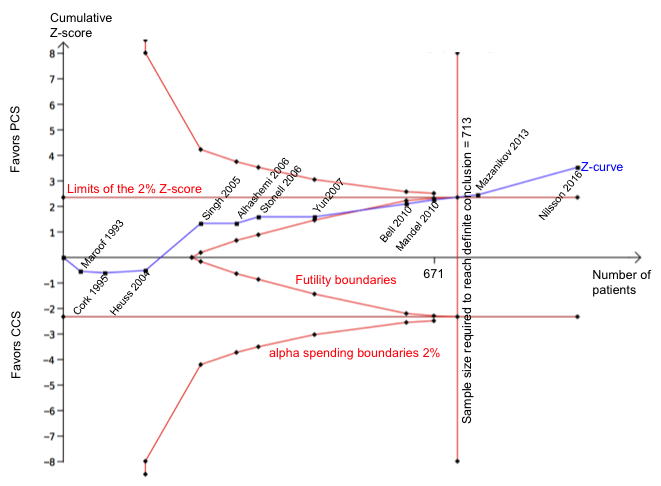
Trial sequential analysis suggests that the sample size required to reach a definitive conclusion on a decrease of 50% in the risk of arterial hypotension using PCS is 957 patients. Therefore, the required sample size is not yet reached with 566 patients, and although the pooled effect from the random effects meta-analysis is statistically significant (blue line crosses the horizontal red line), the Z-curve does not cross the alpha spending boundaries, suggesting that these results may be due to “chance”, and that no definitive conclusion can yet be reached concerning this endpoint.

**Figure F.** Trial sequential analysis for risk of bradycardia. PCS = patient-controlled sedation; CCS = clinician-controlled sedation.



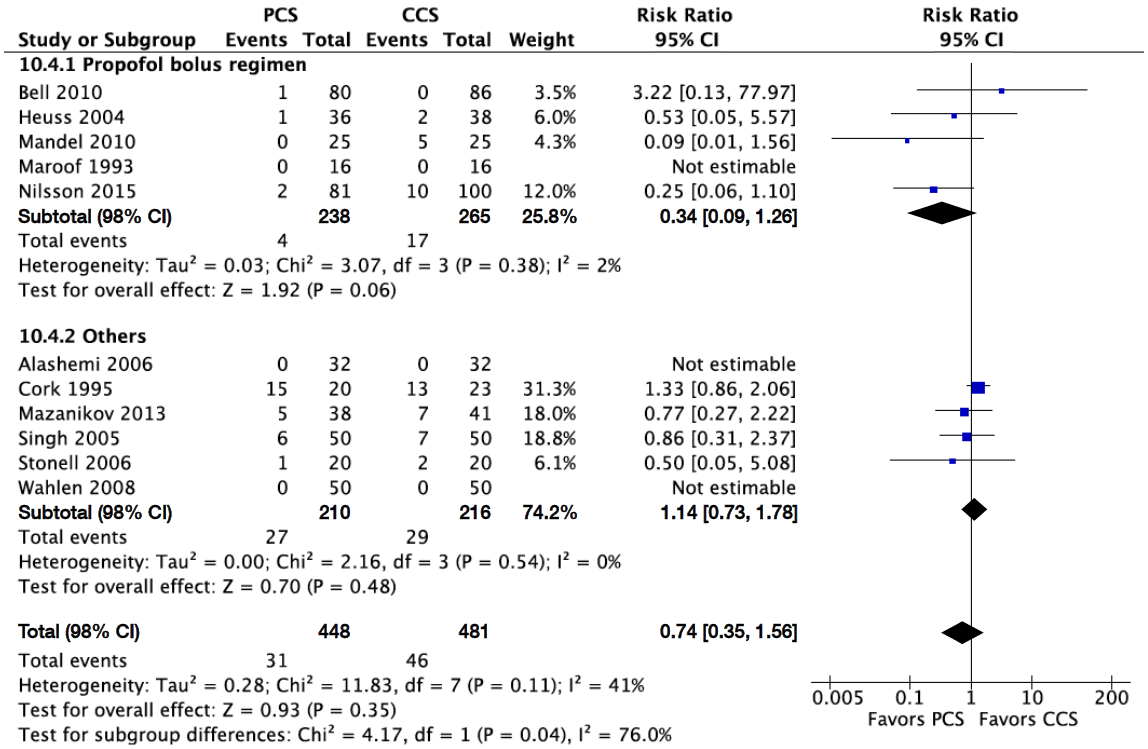
Trial sequential analysis suggests that the sample size required to reach a definitive conclusion on a decrease of 50% in the risk of bradycardia using PCS, is 2319 patients. Therefore, the required sample size is not yet reached with 451 patients. The Z-curve does not cross the alpha spending boundaries and therefore, no definitive conclusion can be reached concerning this endpoint.

**Figure G.** Trial sequential analysis for risk of rescue intervention for adverse event. PCS = patient-controlled sedation; CCS = clinician-controlled sedation.

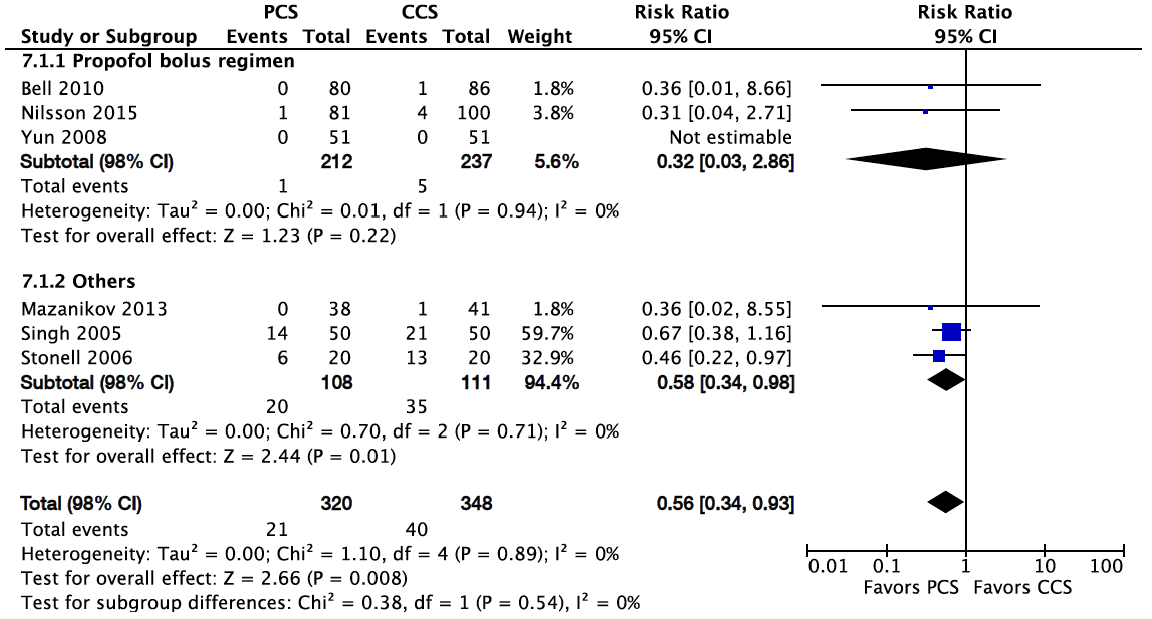


Trial sequential analysis suggests that a sample size of 713 patients is needed to reach a definitive conclusion on a 50% decrease in the risk of requiring a rescue intervention for an adverse event when using PCS compared with CCS. The present analysis has reached the required sample size with 931 patients, suggesting that further trials are unlikely to change our conclusion.

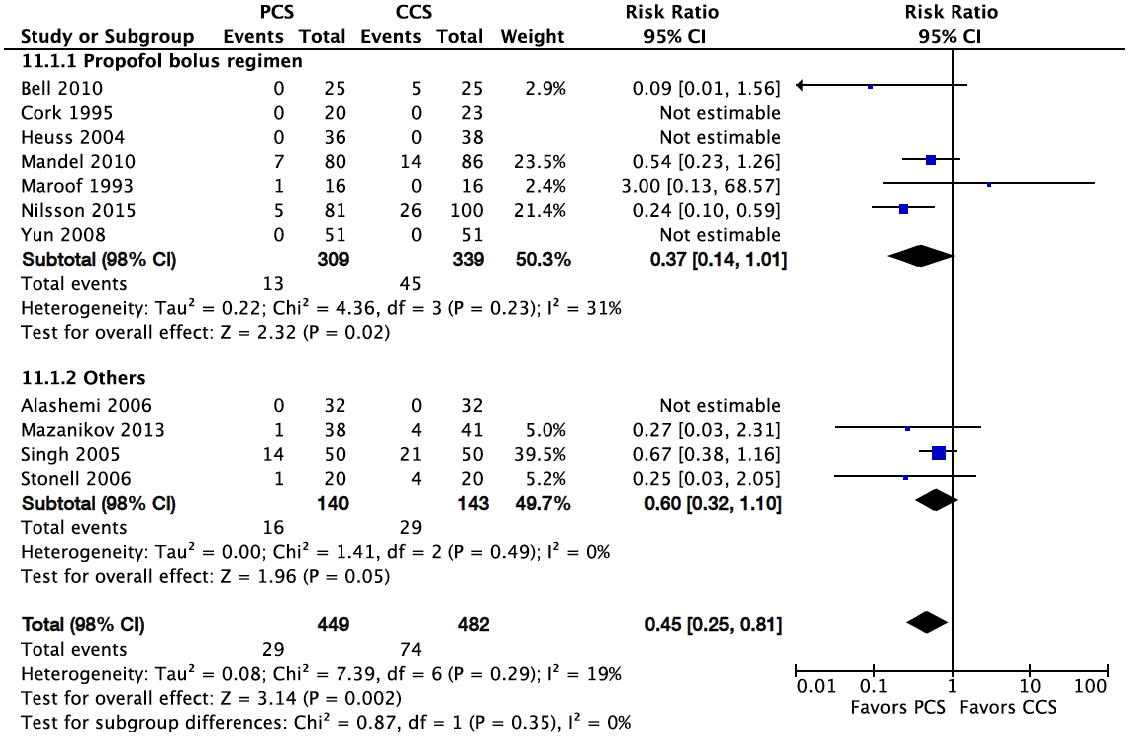
**Figure H.** Risk of oxygen desaturation. Subgroup analysis for trials with propofol bolus regimen in both PCS and CCS groups.PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval.



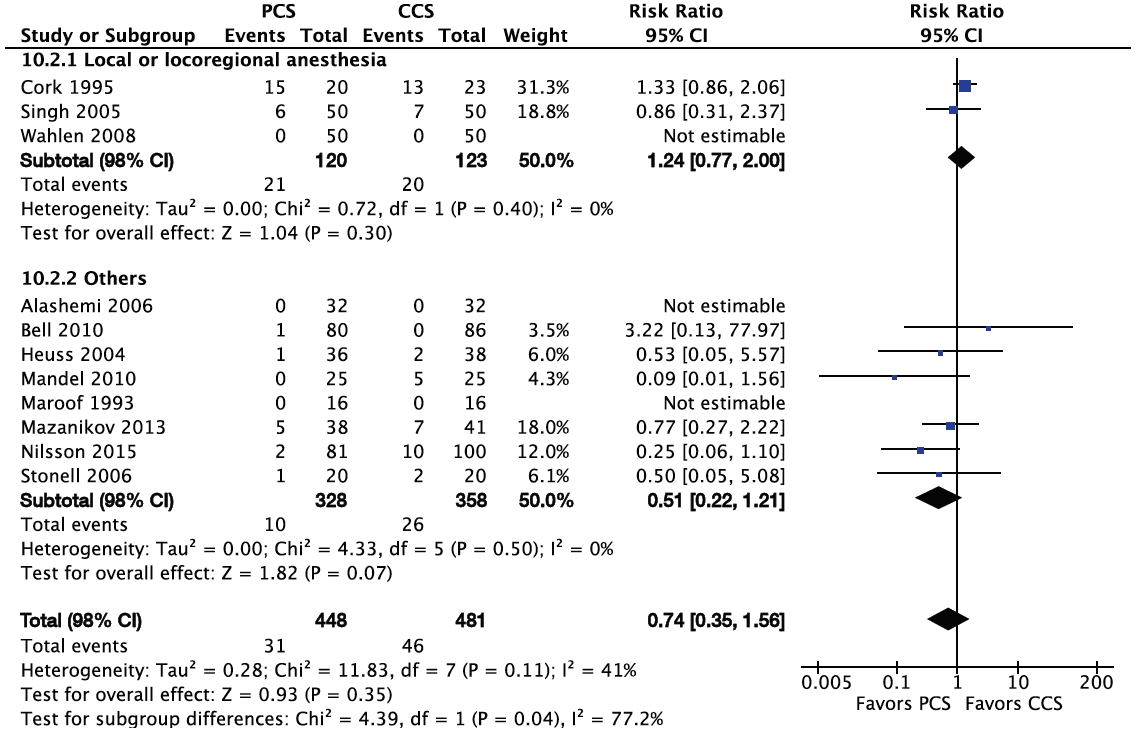
**Figure I.** Risk of arterial hypotension. Subgroup analysis for trials with propofol bolus regimen in both PCS and CCS groups. PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval.



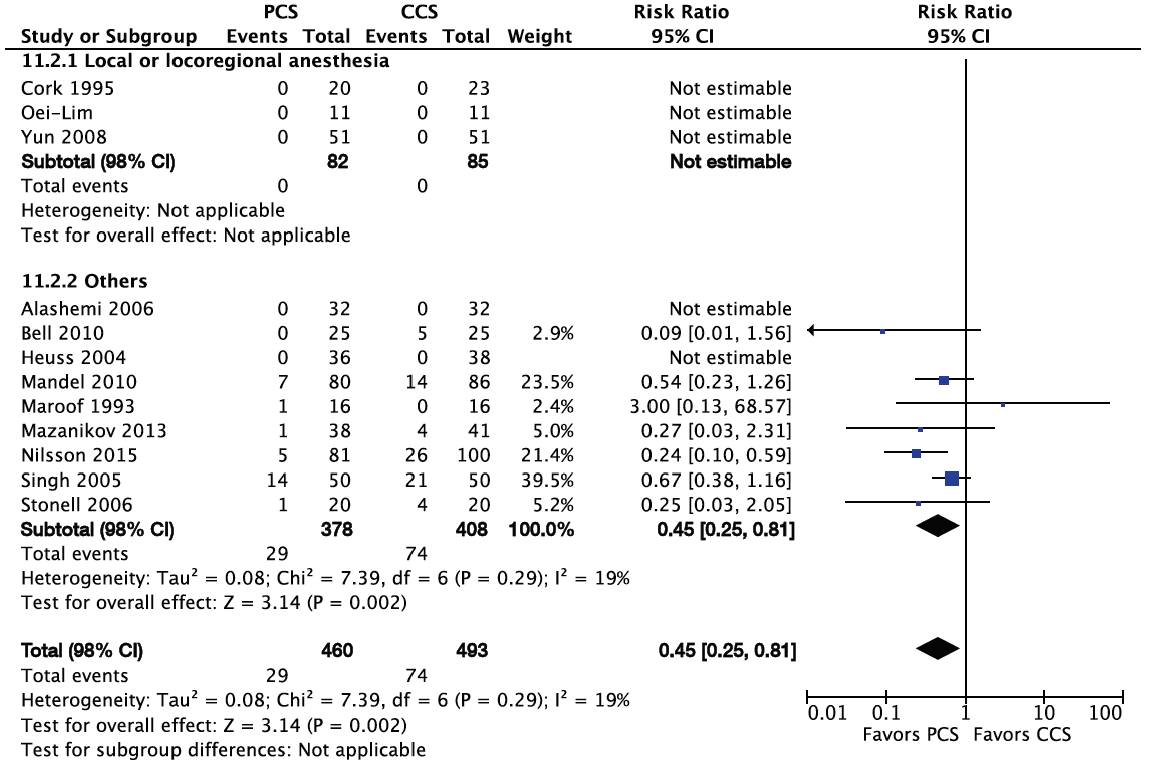
**Figure J.** Risk of rescue intervention for adverse event. Subgroup analysis for trials with propofol bolus regimen in both PCS and CCS groups.PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval.



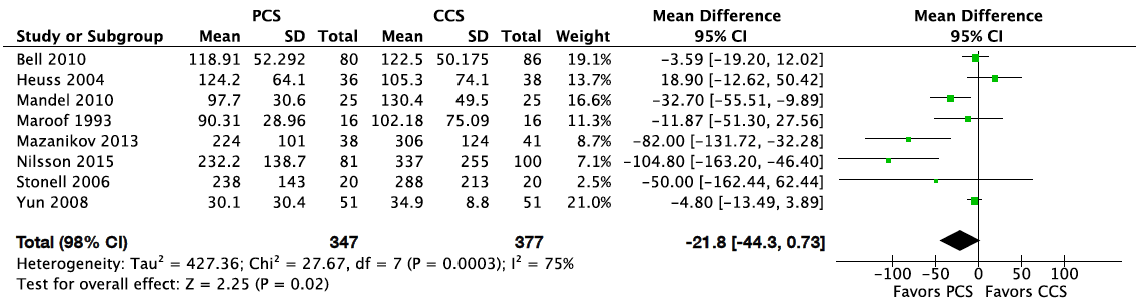
**Figure K.** Risk of oxygen desaturation. Subgroup analysis for trials with local or locoregional anesthesia.PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval.



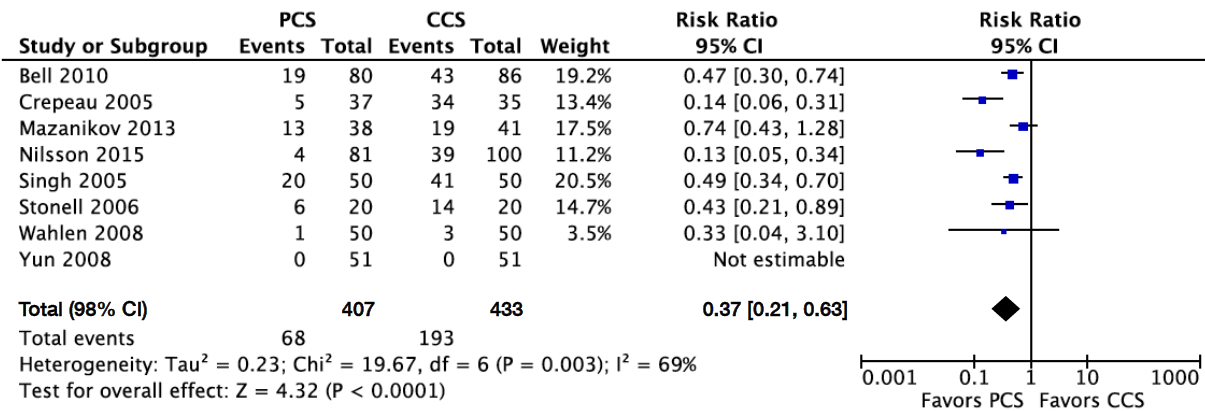
**Figure L.** Risk of rescue intervention for adverse event. Subgroup analysis for trials with local or locoregional anesthesia. PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval.



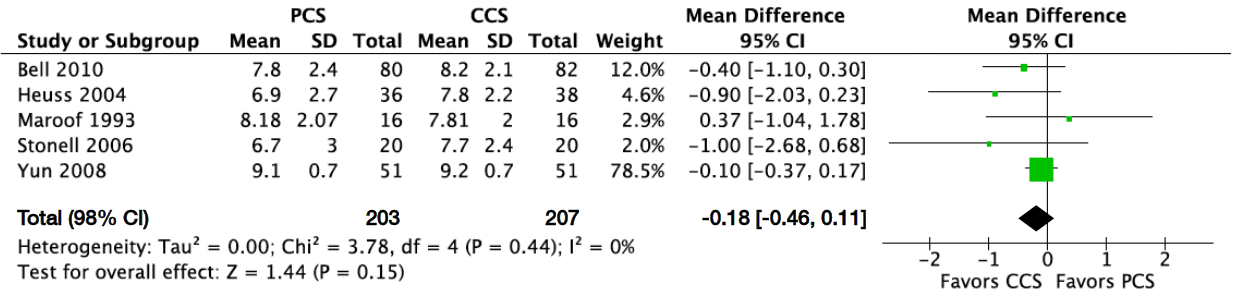
**Figure M.** Total propofol dose**.** PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval, SD = standard deviation.



**Figure N.** Risk of oversedation. PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval.



**Figure O.** Operator satisfaction with sedation. PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval, SD = standard deviation.



**Figure P.** Patient satisfaction with sedation**.** PCS = patient-controlled sedation, CCS = clinician-controlled sedation, CI = confidence interval, SD = standard deviation.

