# Rescue Treatment of Postoperative Nausea and Vomiting: A Systematic Review of Current Clinical Evidence

**Appendix 1: Search strategy**

PubMed

((“PONV”) OR (“Postoperative nausea and vomiting”)) AND ((“rescue”[Title]) OR (“treatment”[Title]) OR (“rescue antiemetic”[Title]) OR (“established”[Title]) OR (“breakthrough”[Title])) NOT (“chemotherapy” [Title])

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((“PONV”) OR (“Postoperative nausea and vomiting”)) AND ((TI “rescue”) OR (TI “treatment”) OR (TI “rescue antiemetic”) OR (TI “established”) OR (TI “breakthrough”)) NOT (TI “chemotherapy”)

Embase

((“PONV”) OR (“Postoperative nausea and vomiting”)) AND ((“rescue”:TI) OR (“treatment”:TI) OR (“rescue antiemetic”:TI) OR (“established”:TI) OR (“breakthrough”:TI)) NOT (“chemotherapy”:TI)

Web of Science:

#1. ALL FIELDS: ('PONV') OR ALL FIELDS: ('Postoperative nausea and vomiting')

#2. TITLE: ('Rescue') OR TITLE: ('treatment') OR TITLE: ('rescue antiemetic') OR TITLE: ('established') OR TITLE: ('breakthrough')

#3. 1 AND 2

**Appendix 2: Level of evidence grading, adapted from ASA Task Force on Acute Pain Management and the Fourth Consensus Guidelines on Management of Postoperative Nausea and Vomiting 12,13**

***Category A: Supportive Literature.***

Randomized controlled trials report statistically significant (p < 0.01) differences between clinical interventions for a specified clinical outcome.

Level 1: The literature contains multiple randomized controlled trials, and aggregated findings are supported by meta-analysis.

Level 2: The literature contains multiple randomized controlled trials, but the number of studies is insufficient to conduct a viable meta-analysis for the purpose of these Guidelines.

Level 3: The literature contains a single randomized controlled trial.

***Category B: Suggestive Literature.***

Information from observational studies permits inference of beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: The literature contains observational comparisons (*e.g.,* cohort, case-control research designs) of clinical interventions or conditions and indicates statistically significant differences between clinical interventions for a specified clinical outcome.

Level 2: The literature contains non-comparative observational studies with associative (*e.g.,* relative risk, correlation) or descriptive statistics.

Level 3: The literature contains case reports.

***Category C: Equivocal Literature.***

The literature cannot determine whether there are beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: Meta-analysis did not find significant differences (p > 0.01) among groups or conditions.

Level 2: The number of studies is insufficient to conduct meta-analysis, and (1) randomized controlled trials have not found significant differences among groups or conditions or (2) randomized controlled trials report inconsistent findings.

Level 3: Observational studies report inconsistent findings or do *not* permit inference of beneficial or harmful relationships.

***Category D: Insufficient Evidence from Literature.***

The *lack* of scientific evidence in the literature is described by the following terms.

Inadequate: The available literature cannot be used to assess relationships among clinical interventions and clinical outcomes. The literature either does not meet the criteria for content as defined in the “Focus” of the Guidelines or does not permit a clear interpretation of findings due to methodological concerns (*e.g.,* confounding in study design or implementation).

Silent: No identified studies address the specified relationships among interventions and outcomes.

**Supplementary Figure 1: Search flowchart**

**Supplementary Figure 2: Risk of bias summary of the included studies**



**Supplementary table 1: characteristics of the included studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Surgical procedure | PONV prophylaxis | NO. patients enrolled | No. patients received intervention | Control | Intervention | Outcome |
| Alon 1998 23 | Surgery under GA (including N2O) | None | 1,513 patients | 314 patients | Placebo | Tropisetron 0.5, 2, or 5 mg  | Further episodes of PONV, additional rescue antiemetic |
| Barton 1975 29 | Surgery under thiopental/ cyclopropane and N2O | None | No separate figure reported | 62 patients | Placebo | Haloperidol 1mg | Vomiting episodes, nausea severity |
| Candiotti 2007 43 | Elective surgery under IA with N2O | Ondansetron 4mg | 250 female patients | 88 patients | Ondansetron 4mg | Granisetron 0.1 or 1mg | CR, additional rescue antiemetic, N&V score |
| Candiotti 2014 44 | Laparoscopic abdominal or gynecological surgery  | Ondansetron4mg | 220 female patients with Apfel score of at least 2 | 98 patients | Ondansetron 4mg  | Palonosetron 0.075 mg | CR, additional rescue antiemetic, adverse reaction |
| Candiotti 2019 46 | Elective surgeries under IA | No prophylaxis | 1,988 patients | 560 patients | Placebo | 5mg or 10mg amisulpride | CR, additional rescue antiemetic, N&V score, AE |
| Choi 2018 19 | Elective laparoscopic surgery under IA | None | 610 patients | 210 patients | Ondansetron 4mg | Ramosetron 0.3mg | CR, PONV incidence, additional rescue antiemetic requirement |
| Chung 1999 17 | Surgery under regional or GA | None | 4511 patients | 1366 patients | Ondansetron 8mg | Ondansetron 16mg or metoclopramide 10mg | CR, AE |
| Claybon 1994 14 | Surgery under GA (including N2O) | None | 2,812 patients | 866 patients | Placebo | Ondansetron 1, 4, 8mg | Further episodes of PONV |
| Coloma 2002 56 | Laparoscopic surgery with IA with N2O | Metaclopramide 10mg or droperidol 0.625mg | 268 patients | 90 patients | Ondansetron 4mg | PC6 acustimulation or ondansetron plus acustimulation | N&V episodes, additional rescue antiemetic, quality of recovery score |
| Cotton 2007 38 | Laparoscopic gynecological surgery under IA with N2O | None | 100 female patients (28 excluded for protocol violation) | 72 patients | Ondansetron 4-8mg | Isopropylalcohol 70% | Time to 50% reduction of PONV severity, additional antiemetic requirement |
| Cronin 2015 51 | Ambulatory laparoscopic procedures | Scopolamine, ondansetron or dexamethasone | 250 female patients | 102 patients | Breathing exercise | Breathing exercise plus isopropylalcohol | Nausea score, additional antiemetic requirement |
| Dabbous 2001 26 | Laparoscopic surgeries | None | No separate figure reported | 173 patients | Ondansetron 4 mg | Droperidol 1.25 mg or metoclopramide 10 mg | PONV score, additional rescue antiemetic, adverse event |
| Dabbous 2012 81 | Elective surgery under IA plus N2O | None | No separate figure reported | 44 patients with 1-2 Apfel risk factors | Metoclopramide 10mg | Naloxone 0.5mcg/kg | CR, Partial response (significantly improved nausea severity) |
| Darvall 2017 53 | Laparoscopic or breast surgery | 0-2 antiemetics including dexamethasone and droperidol | 94 female patients | 25 patients | Ondansetron 4mg | Sugar free peppermint chewing gum | Full resolution, time to full resolution, further antiemetic treatment |
| Deitrick 2015 34 | Ambulatory surgery patients | None or ondansetron and/or dexamethasone | 352 female and 271 male patients | 120 patients, mostly female | Promethazine 12.5mg | Promethazine 6.25mg | Additional rescue antiemetic, nausea severity, sedation |
| Diemunsch 1997 30 | Surgery under IA | None | 2032 patients | 746 patients | Ondansetron 4mg | Metoclopramide 10mg  | Further episodes of PONV, additional rescue antiemetic, patient satisfaction, adverse reactions |
| Diemunsch 1999 35 | Gynecological surgery | None | No separate figure reported | 36 patients | Vofopitant 25mg | Placebo | Vomiting episodes, nausea severity |
| Du Pen 1992 18 | Surgery under IA and N2O | None | No separate figure reported | 500 patients | Placebo | Ondansetron 1, 4, 8mg | CR |
| Gan 1999 36 | Ambulatory surgery with IA and N2O | None | 200 patients | 69 patients | Placebo | Propofol 20 or 40mg with 5 minute lockout | CR, additional rescue antiemetic, PACU discharge time, Patient satisfaction |
| Habib 2019 8 | Elective surgeries under IA | 1-3 antiemetics including ondansetron, granisetron, dexamethasone and scopolamine | 2,295 patients | 702 patients | Placebo | 5mg or 10mg amisulpride | CR, additional rescue antiemetic, N&V score  |
| Habib\* 2005 47 | Day surgery under GA | Ondansetron, droperidol or nothing | No separate figure reported | 431 patients, mostly female | Ondansetron 4mg | Droperidol 0.625-1.25mg, metoclopramide 10mg, promethazine 6.5-25mg, and dimenhydrinate 25-50mg | CR |
| Habib\* 2007 48 | Surgery under IA and N2O | Ondansetron | No separate figure reported | 4391 patients | Ondansetron | Promethazine | CR, PONV score, PACU discharge time |
| Hahm 2015 24 | Elective laparoscopic surgery under IA with N2O | None | No separate figure reported | 152 patients with history of PONV, motion sickness or expected intraoperative opioid use | Placebo | Palonosetron 0.075mg | C, incidence of nausea and vomiting, additional rescue antiemetic requirement |
| Harper 1998 37 | Gynecological laparoscopic procedures under IA and N2O | None | 77 patients | 48 patients | Placebo | Propofol 3mg, 9mg or 27mg | Nausea score, additional antiemetic requirement, further vomiting episodes |
| Heidari 2011 58 | Cholecystectomy under IA and N2O | None | No separate figure reported | 132 patients | Metoclopramide, up to 10mg | Midazolam up to 2mg, or both | Nausea and vomiting incidences |
| Hunt 2013 40 | Elective surgery under GA | None | 1,151 patients | 301 patients | Saline | Aromatherapy with ginger, alcohol, blended essential oil  | PONV score, additional rescue antiemetic |
| Jabalameli 2012 57 | Elective cesarean delivery under spinal anesthesia | None | No separate figure reported | 132 patients | Midazolam 30 μg/kg | Ondansetron 8 mg or ondansetron plus midazolam | PONV score, additional rescue antiemetic |
| Karaman 2019 41 | Elective surgery under GA | None | 5,205 patients | 184 patients | Placebo | Ginger, lavender or rose aromatherapy | PONV score, additional rescue antiemetic requirement |
| Khalil 1996 16 | Surgery under IA and N2O | None | 2,720 children between ages of 2 and 12 | 375 children  | Placebo | Ondansetron 0.1mg/kg up to 4mg | CR, additional antiemetic requirement, further vomiting episodes, PACU LOS, AE |
| Kovac 199721  | Elective ambulatory surgery IA and N2O  | None | 1557 patients | 620 patients | Placebo | Dolasetron 12.5 mg to 100mg | CR, AE |
| Kovac 1999 3 | Ambulatory surgery under IA with N2O | Ondansetron 4mg | 2,199 patients | 428 patients | Placebo | Ondansetron 4mg | CR, nausea severity, additional rescue antiemetic |
| Kranke 2014 49 | Elective surgery under GA | Ondansetron 4mg | 527 patients with Apfel score of at least 3 | 130 patients  | Ondansetron 4mg  | Vestipitant 4, 6, 12, 18, 24, or 36 mg  | CR, additional rescue antiemetic, treatment failure |
| Lacroix 1996 28 | Surgery under IA | None | 859 patients | 78 patients | Propofol 10mg,  | Droperidol 1.25 mg or metoclopramide 10 mg | Further episodes of PONV, additional rescue antiemetic, AE |
| Larijani 1991 42 | Surgery under thiopental and N2O anesthesia | Scopolamine 0.4mg | 229 patients | 36 patients | Placebo | Ondansetron 8mg | CR, vomiting episodes |
| Merritt 2002 39 | Surgery under GA | None | 111 patients | 39 patients | Standard antiemetic | Isopropylalcohol 70% | Treatment failure, Nausea score |
| Meyer 2005 22 | Ambulatory surgery under IA | 25% of patients received PONV prophylaxis | 559 patients | 92 patients | Ondansetron 4mg | Dolasetron 12.5mg | Additional antiemetic requirement, further vomiting episodes, unplanned admission, PACU LOS |
| Munoz 2006 27 | All surgical patients | none | No separate figure reported | 120 patients | Ondansetron 2mg | Dexamethasone 8mg or droperidol 1.25mg | CR |
| Ormel 2011 55 | Gynecological day surgery | Dexamethasone 8mg, Ondansetron 4mg, Droperidol 0.625mg or placebo | 343 patients | 80 patients | Ondansetron 4mg, Droperidol 0.625mg  | Dexamethasone 8mg, Ondansetron 4mg, Droperidol 0.625mg  | PONV score, additional rescue antiemetic |
| Pellegrini 2009 50 | Elective surgery under IA | Ondansetron 4mg | 96 patients (11 withdrew from the study) | 85 patients with 2 Apfel risk factors | Promethazine 12.5 or 25mg | Isopropylalcohol 70% | Time to 50% reduction of PONV severity |
| Polati 1997 31 | Gynecological laparoscopy under IA with N2O | None | 378 female patients | 175 patients | Placebo | Metoclopramide 10mg or ondansetron 4mg | Further episodes of PONV |
| Rusch 2007 54 | Elective surgery under GA | 0-2 antiemetics including dexamethasone and ondansetron | 1,800 patients | 242 patients | Dolasetron 12.5mg | Haloperidol 0.75mg, Dolasetron with dexamethasone 8mg, Haloperidol with 8mg dexamethasone | Further episodes of vomiting, AE |
| Scuderi 1993 15 | Surgery under IA and N2O | None | 1,346 patients | 500 patients | Placebo | Ondansetron 1mg, 4mg, 8mg | CR, vomiting episodes |
| Sites 2014 52 | Ambulatory surgery under GA | Ondansetron, metoclopramide and/or dexamethasone | 196 patients | 42 patients | Controlled breathing | Peppermint aromatherapy | Nausea score, additional antiemetic requirements |
| Stienstra 1997 25 | Gynecological surgery under IA and N2O | None | No separate figure reported | 74 female patients | Ondansetron 8mg | Droperidol 1 mg or alizapride 100 mg  | Further episodes of PONV, additional rescue antiemetics, PONV score |
| Taylor 1997 20 | Surgery under IA and N2O | None | No separate figure reported | 519 patients | Placebo | Granisetron 0.1mg, 1mg or 3mg | Further episodes of PONV, additional rescue antiemetic |
| Yazbeck-Karam 2017 45 | Elective surgery under GA | 0-2 antiemetics including dexamethasone and ondansetron | 450 patients | 112 patients, mostly female | ondansetron 4mg  | haloperidol 1mg  | PONV free period, QTc change |

\*: retrospective studies, AE: adverse events, CR: complete response, GA: general anesthesia, IA: inhalational anesthesia, LOS: length of stay, PACU: post-anesthesia care unit, PONV: postoperative nausea vomiting

**Supplementary table 2: Risk of bias gradings**

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| **Alon 1999** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized and provided as coded and identical appearing vials |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Barton 1975** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are provided as coded identical containers |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| **Candiotti 2019** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized, provided as coded and identical appearing vials |
| Deviation from intended intervention | Low | Patients and clinicians blinded, deviations are evenly distributed across all interventions |
| Missing Outcome data | Low | Less than 5% participant attrition |
| Measurement of outcome | Low | Blinded investigator |
| Selection of reported results | Low | NCT02449291 |
| Overall | Low |  |

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| --- | --- | --- |
| **Candiotti 2014** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Allocation concealment not reported |
| Deviation from intended intervention | Some concerns | Clinician nor patient blinded |
| Missing Outcome data | Some concerns | Open label study, one patient was removed by sponsor decision |
| Measurement of outcome | Some concerns | Investigator not blinded |
| Selection of reported results | Low | NCT00967499 |
| Overall | High |  |

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| --- | --- | --- |
| **Candiotti 2007** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are randomized and provided as coded and identical appearing vials |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concerns | Consort diagram not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Choi 2018** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Sone concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Low | 4 out of 210 patients excluded |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Low | NCT03017222 |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Chung 1999** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Allocation concealment not reported |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Claybon 1994** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Some concerns | Patient blinded, clinician blinding not clear, significnat proportion of protocol deviation |
| Missing Outcome data | High | 156 out of 1022 patients did not follow protocol |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | High |  |

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| --- | --- | --- |
| **Coloma 2002** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concern | Allocation concealment not reported |
| Deviation from intended intervention | Low | Patient and clinician blinded |
| Missing Outcome data | Some concern | 7 out of 90 patients who developed PONV had data missing |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Cotton 2007** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Some concerns | 28 out of the initial 100 patients were excluded due to protocol deviation |
| Missing Outcome data | Some concerns | 28 out of the initial 100 patients were excluded due to protocol deviation |
| Measurement of outcome | Some concerns | Investigator blinding not specified |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | High |  |

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| **Cronin 2015** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | High | Allocation was determined by month of surgery, significantly more smokers in the IPA cohort |
| Deviation from intended intervention | Some concerns | Patient not blinded, no protocol deviation |
| Missing Outcome data | Some concerns | 19 out of 102 patients excluded |
| Measurement of outcome | Some concerns | Investigator not blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | High |  |

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| --- | --- | --- |
| **Dabbous 2012** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Dabbous 2001** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concern | Allocation concealment not reported |
| Deviation from intended intervention | Low | Patient and clinician blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Darvall 2017** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Computer randomization and sealed envelope allocation concealment |
| Deviation from intended intervention | Some concerns | Patient and clinician blinding not clear, no protocol deviation |
| Missing Outcome data | Low | No treated patient was lost to follow up |
| Measurement of outcome | Some concerns | Investigator blinding not specified |
| Selection of reported results | Low | ACTRN12615001327572 |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Deitrick 2015** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized and provided as coded and identical appearing syringes |
| Deviation from intended intervention | Low | Patient and clinician blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Diemunsch 1999** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Investigator blinded |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Diemunch 1997** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concern | Allocation concealment not reported |
| Deviation from intended intervention | Low | Patient blinded, clinician blinding not clear, no protocol deviation |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Du Pen 1992** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Gan 1999** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are provided as coded and identical appearing syringes |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Habib 2019** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized, provided as coded and identical appearing vials |
| Deviation from intended intervention | Low | Patients and clinicians blinded, deviations are evenly distributed across all interventions |
| Missing Outcome data | Low | Less than 5% participant attrition |
| Measurement of outcome | Low | Blinded investigator |
| Selection of reported results | Low | NCT02646566 |
| Overall | Low |  |

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| --- | --- | --- |
| **Habib 2007** |  |  |
| Domain | Risk of bias | Justification |
| Confounding | Some concerns | Promethazine cohort had more female patients |
| Participant selection | Low | Patients with PONV after prophylaxis were included |
| Intervention classification | Low | Intervention classified according to rescue antiemetic given |
| Deviation from intended interventions | Low | Intervention classified according to rescue antiemetic given |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcomes | Some concerns | Blinding of investigators to the rescue antiemetic choice not specified |
| Selection of reported results | Some concerns | Protocol is not registered |
| Overall | High |  |

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| --- | --- | --- |
| **Habib 2005** |  |  |
| Domain | Risk of bias | Justification |
| Confounding | Low | Baseline and surgical risk factor for PONV is comparable, patients stratified according to the prophylaxis received |
| Participant selection | Low | Patients with PONV after prophylaxis were included |
| Intervention classification | Low | Intervention classified according to rescue antiemetic given |
| Deviation from intended interventions | Low | Intervention classified according to rescue antiemetic given |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcomes | Some concerns | Blinding of investigators to the rescue antiemetic choice not specified |
| Selection of reported results | Some concerns | Post hoc analysis, protocol not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Hahm 2015** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are provided as coded identical containers |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Low | 6 out of 152 randomized patients were excluded |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Low | NCT01568268 |
| Overall | Low |  |

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| --- | --- | --- |
| **Harper 1998** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are provided as coded identical containers |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Hunt 2013** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment process not described |
| Deviation from intended intervention | Some concerns | Patient and clinician not blinded, 2 protocol deviation due to aromatherapy degredation |
| Missing Outcome data | Some concerns | No consort diagram |
| Measurement of outcome | Some concerns | Investigator blinding not specified |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | High |  |

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| --- | --- | --- |
| **Jabalameli 2012** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized, coded and provided as identical appearing vials |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concerns | No consort diagram |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Karaman 2020** |  |  |
| Domain | Risk of bias |  |
| Randomization process | Low | Allocation made after patient develops PONV, randomization using table |
| Deviation from intended intervention | Some concerns | Patient not blinded, no protocol deviation |
| Missing Outcome data | Low | All randomized patients were analysed |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Low | NCT02732379 |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Khalil 1996** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are provided as coded identical containers |
| Deviation from intended intervention | Low | Patient blinded, 12 protocol violation out of 375 participants |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Kovac 1997** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are provided as coded identical containers |
| Deviation from intended intervention | Low | Patient and clinician blinded |
| Missing Outcome data | Some concerns | No CONSORT data |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some | Trial not registered |
| Overall | Some Concerns |  |

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| --- | --- | --- |
| **Kovac 1999** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Allocation concealment not reported |
| Deviation from intended intervention | Low | Patient and clinician blinded |
| Missing Outcome data | Some concerns | No CONSORT data |
| Measurement of outcome | Some concerns | Investigator blinding not specified |
| Selection of reported results | Low | Glaxo Wellcome Protocol S3AA4001 |
| Overall | Some Concerns |  |

|  |  |  |
| --- | --- | --- |
| **Kranke 2014** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment process not described |
| Deviation from intended intervention | Low | Patient and clinician blinded, no protocol deviation |
| Missing Outcome data | Low | No treated patient was lost to follow up |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Low | NCT01507194 |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Lacroix 1996** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized and provided as coded and identical appearing syringes |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Lairjani 1991** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Allocation concealment not reported |
| Deviation from intended intervention | Low | Patient blinded |
| Deviation from intended intervention | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Merritt 2002** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | High | Allocation was determined by date of surgery, control group had significantly more females |
| Deviation from intended interventions | Some concerns | Patient and clinician blinding not clear, no protocol deviation reported |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcomes | Some concerns | Investigator blinding not specified |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | High |  |

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| --- | --- | --- |
| **Meyer 2005** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized and provided as coded and identical appearing syringes |
| Deviation from intended intervention | Low | Patient and clinician blinded |
| Missing Outcome data | Low | No patients excluded |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial registered in a closed registry |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Morteza Hidari 2012** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized and provided as coded and identical appearing syringes |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Munoz 2006** |  |  |
| Domain | Risk of bias |  |
| Randomization process | Some concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Ormel 2011** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized, provided as coded and identical appearing vials |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concerns | 22 of the original 337 patients excluded |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Pelligrini 2009** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Randomization and allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Some concerns | Patient not blinded, no protocol deviation |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Some concerns | Investigator blinding not specified |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | High |  |

|  |  |  |
| --- | --- | --- |
| **Polati 1997** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concern | Allocation concealment not reported |
| Deviation from intended intervention | Low | Patient blinded, clinician blinding not clear |
| Missing Outcome data | Some concerns | 22 patients excluded, further 18 patients with PONV was excluded |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Rusch 2007** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized and provided as identical appearing vials |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concerns | No consort data |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Scuderi 1993** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Allocation concealment procedures not reported, cohorts characteristics are balanced  |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | CONSORT diagram/ missing data report not available |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Sites 2014** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Some concerns | Allocation concealment procedures not reported |
| Deviation from intended intervention | Some concerns | Protocol deviation resulted in the exclusion of 22 out of 330 patients |
| Missing Outcome data | Some concerns | 134 out of 330 patients excluded |
| Measurement of outcome | Some concerns | Investigator blinding not clear |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | High |  |

|  |  |  |
| --- | --- | --- |
| **Steinstra 1997** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are block randomized and provided as coded and identical appearing vials |
| Deviation from intended intervention | Low | Patient and clinician blinded |
| Missing Outcome data | Some concerns | No consort data |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

|  |  |  |
| --- | --- | --- |
| **Taylor 1997** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Study substances are randomized and provided as coded and identical appearing syringes |
| Deviation from intended intervention | Low | Patient blinded |
| Missing Outcome data | Some concerns | 53 out of 519 patients excluded from analysis |
| Measurement of outcome | Low | Investigator blinded |
| Selection of reported results | Some concerns | Trial not registered |
| Overall | Some concerns |  |

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| --- | --- | --- |
| **Yazbeck-Karam 2017** |  |  |
| Domain | Risk of bias | Justification |
| Randomization process | Low | Computer randomization and sealed envelope allocation concealment |
| Deviation from intended intervention | Low | Patient and clincian blinded |
| Missing Outcome data | Some concern | 7 out of 120 patients excluded due to incomplete data |
| Measurement of outcome | Low | Inestigator blinded |
| Selection of reported results | Low | NCT02143531 |
| Overall | Some concern |  |

**Supplementary table 3: Factors associated with failed PONV prophylaxis**

|  |  |  |  |
| --- | --- | --- | --- |
|  | PONV prophylaxis | factors associated with failed prophylaxis | Comments |
| Larijani 1991 39 | Scopolamine 0.4mg | Female gender (OR 4.8895 % CI: 1.8 to 12.9) | No other variables were investigated |
| Kovac 1999 3 | Ondansetron 4mg | Female gender (OR 2.09, 95 % CI: 1.60 to 2.71)History of motion sickness (1.80, 95 % CI: 1.42 to 2.26)History of PONV (OR 2.30,95 % CI: 1.80 to 2.95) | Multivariable analysis were not conducted |
| Candiotti 2007 40 | Ondansetron 4mg | Not reported |  |
| Candiotti 2014 41 | Ondansetron 4mg | Not reported |  |
| Yazbeck-Karam 2017 42 | 0-2 antiemetics including dexamethasone and ondansetron | Not reported |  |
| Habib 2019 8 |  | Not reported |  |
| Kranke 2014 44 | 4mg ondansetron | Not reported |  |
| Pellegrini 2009 45 | 4mg ondansetron | Not reported |  |
| Sites 2014 47 | Ondansetron, metoclopramide and/or dexamethasone | Female gender (p<0.01), but not any other Apfel score criteria was associated with failed prophylaxis | Raw data was not published |
| Darvall 2017 48 | 0-2 antiemetics including dexamethasone and droperidol | Not reported |  |