

Dexamethasone for the prevention of postoperative nausea and vomiting in children undergoing non-cardiac surgery: a systematic review and meta-analysis

Qihong Shen (✉ shenqihong1989@163.com)

First Affiliated Hospital of JiaXing University <https://orcid.org/0000-0003-3365-779X>

Hui-fang Li

TongXiang Maternal and Child Health Care

Xu-yan Zhou

First Affiliated Hospital of JiaXing University

Xiao-zong Yuan

First Affiliated Hospital of JiaXing University

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Abstract

BACKGROUND: Postoperative nausea and vomiting (PONV) is a frequent and distressing complication of general anaesthesia in paediatric patients. Dexamethasone was reported to prevent PONV in previous randomized controlled trials (RCTs). The purpose of this meta-analysis was to evaluate the role of dexamethasone in the prevention of PONV in children undergoing non-cardiac surgery. **METHODS:** PubMed, EMBASE, the Cochrane Library, and Web of Science were searched to identify randomized trials that reported the efficacy of perioperative dexamethasone in paediatric non-cardiac surgical patients. **RESULTS:** Fourteen randomized controlled trials that included 1700 children were included. Compared with placebo, dexamethasone showed a lower incidence of PONV by intravenous injection (RR 0.38, 95% confidence interval (CI) 0.30–0.49) and by local infiltration (RR 0.58, 95% CI 0.34–0.99). The combination of dexamethasone and a 5-HT₃ receptor antagonist was more effective than the 5-HT₃ antagonist or dexamethasone alone in preventing PONV. **CONCLUSION:** Perioperative dexamethasone was an effective measure with few complications for preventing PONV in children after non-cardiac surgery.

Background

Among paediatric surgery patients, the incidence of PONV is as high as 70% without prophylactic antiemetics [1]. A search suggested that the risk factors for PONV in children were age, anaesthetic effective time, different types of surgery, motion sickness and personal history[2]. PONV is an unpleasant result of surgery and anaesthesia, causing dehydration, electrolyte imbalance, and psychiatric disorders, and prolonging hospital length of stay[3-5]. Therefore, it is urgent to find an effective way to reduce the incidence of adverse reactions.

Various measures have been reported to prevent and treat PONV, including intraoperative liberal fluid therapy and total intravenous anaesthesia[6, 7]. Nevertheless, no conclusive studies support pharmacological prophylaxis. Several studies have reported that preoperative dexamethasone can effectively prevent PONV after tonsillectomy[8, 9]. In another RCT, patients with dexamethasone intervention had a significantly lower incidence of nausea and vomiting within 24 hours than patients who received placebo[10]. A meta-analysis reported that dexamethasone in combination with serotonin type 3 (5-HT₃) receptor antagonists in children undergoing strabismus surgery is recommended[11]. However, no similar review focusing on other types of surgery could be found. The safety for children received dexamethasone is still unclear. Therefore, we determined the effectiveness of dexamethasone in preventing PONV in non-cardiac surgery children by conducting this systematic review and meta-analysis.

Methods

The reporting of this systematic review and meta-analysis follows the PRISMA recommendations[12]. Our meta-analysis does not yet have a registered protocol.

Systematic Literature Search

We performed a meta-analysis of RCTs that investigated the effectiveness of dexamethasone in preventing PONV in comparison with that in controls. Studies combining dexamethasone and other drugs were included, provided that the only difference between the groups was the use of dexamethasone.

Two independent investigators (Li and Zhou) searched PubMed, EMBASE, the Cochrane Library, and Web of Science to find available RCTs from database establishment to November 30, 2018. Supplemental Digital Content describes PubMed's search strategy using subject words plus free words. Only English databases were searched. We also manually retrieved relevant studies, including complementary medical textbooks and clinical guidelines, for all relevant tests, and we contacted the experts in the field and the corresponding authors to obtain important information that was not available during retrieval.

Selection Criteria and Data Extraction

Studies meeting the following criteria were included: (1) randomized controlled trial comparing dexamethasone as a PONV prophylactic agent versus a control, (2) patients <18 years of age, (3) description of the dosing regimen of dexamethasone and anaesthesia method, (4) evaluation of nausea and vomiting after general anaesthesia, and (5) published in English. The exclusion criteria included (1) cardiac surgery patients, (2) dexamethasone was administered orally, and (3) duplicate publications.

Two reviewers independently extracted the following items from the included studies: name of the first author, year of publication, age of patients, surgical type, sample size, anaesthetic techniques, incidence of nausea and vomiting, use of rescue antiemetic, and complications. A conflict of opinion was resolved by a third reviewer (Yuan).

Statistical Analysis

The meta-analysis was conducted using RevMan 5.3. For dichotomous outcomes, we calculated a pooled risk ratio (RR) and 95% confidence intervals (CIs) based on random and fixed effect models. Heterogeneity of trials was assessed by I^2 . If $I^2 < 50\%$, the fixed effects model was used. If significant heterogeneity ($P \leq 0.1$ or $I^2 \geq 50.0\%$) was identified, we sought its source by subgroup or sensitivity analysis. We calculated the number needed to treat (NNT) as an estimate of the clinical impact of the intervention.

The primary outcome was the incidence of PONV. The number of patients using rescue antiemetics and the incidence of adverse effects, such as headache, dizziness, and sedation, were secondary outcomes in the systematic review. Three RCTs[13-15] evaluated PONV according to a numeric scoring system (0 = no nausea or vomiting, 1 = nausea but no vomiting, 2 = vomiting once in 30 min or more, 3 = persistent nausea (>30 min) or two or more vomits in 30 min), as proposed by Subramaniam et al. The meta-analysis was conducted for the presence of vomiting in patients with a PONV score of 2 and 3 points.

Results

Search Results

The search process is shown in Figure 1. Initially, 2701 relevant studies were identified. After excluding duplicate studies, we screened 978 studies on the basis of abstracts. Then, 47 full-text articles were assessed for eligibility. An additional 33 articles were excluded on the following basis: dexamethasone not utilized as the primary intervention; included an adult patient; were not published in English, were not RCTs; and no data on outcomes of interest. Finally, 14 studies[8-10, 13-23] were included in our meta-analysis. All authors endorsed the included studies. A funnel plot analysis was performed for outcomes involving 10 or more studies.

Assessment of Quality and Bias

The summary of risk of bias is shown in Figure 2. Most of the studies described random sequence generation, allocation concealment and blinding of participants and personnel. All outcome assessments were blinded. No incomplete outcome data, selective reporting or other biases were reported.

Characteristics of Included Studies

Overall, 14 randomized controlled trials met our inclusion criteria, and a total of 1700 paediatric patients were included in this meta-analysis. Table 1 shows the characteristics of the included studies regarding the year of publication, age, sample size, surgery type, interventions, and anaesthetic techniques.

Dexamethasone Versus Placebo

Dexamethasone Intravenous Injection and Rescue Antiemetic

Six studies[8, 10, 13, 15, 17, 19] reported the incidence of POV in the dexamethasone and placebo groups. In the Madan study[13], dexamethasone was compared at three different doses (0.25, 0.5, 1.0 mg/kg), and we selected all groups as dexamethasone groups for meta-analysis because dexamethasone in other studies was administered at doses ranging from 0.15 mg/kg to 1.0 mg/kg. The difference was significant in favour of the dexamethasone group (RR 0.38, 95% CI 0.30–0.49, $P < 0.01$; NNT = 2.54; $n = 641$; Figure 3). No substantial heterogeneity existed among the studies ($P=0.30$, $I^2 = 18\%$). Therefore, a fixed effect model was adopted.

Four studies[8, 10, 15, 19] reported the incidence of PON between the dexamethasone and placebo groups. The results showed that the incidence of PON in the dexamethasone group was significantly lower than that in the placebo group (RR 0.40, 95% CI 0.27-0.59, $P<0.01$; NNT =4.40; $n =415$; Figure 3).

Only one of the included RCTs[9] compared the difference between dexamethasone and placebo in preventing PONV. The incidence of PONV was 2 of 25 patients and 1 of 25 patients, suggesting that no difference existed in the 2 groups. However, Giannoni et al. evaluated nausea or vomiting in the first 4 hours postoperatively, while others showed the incidence over a 24-hour period. Three trials[8, 13, 15]

reported that the number of patients requiring rescue antiemetics was significantly lower in the dexamethasone group (RR 0.27, 95% CI 0.18–0.41, $I^2=0\%$; Figure 3) than that in the placebo group.

Dexamethasone Local Infiltration

Three studies[8, 16, 18] reported that dexamethasone was administered by local infiltration. The result showed that dexamethasone was favoured for preventing PONV (RR 0.58, 95% CI 0.341–0.99, $I^2=0\%$; Figure 4).

Dexamethasone Combine 5-HT3 Receptor Antagonist Versus 5-HT3 Receptor Antagonist

Three studies [14, 20, 23] compared dexamethasone plus a 5-HT3 receptor antagonist with 5-HT3 receptor antagonist alone for the prevention of POV. Analysis showed that dexamethasone combined with a 5-HT3 receptor antagonist was significantly better than the 5-HT3 receptor antagonist alone in preventing POV (RR 0.25, 95% CI 0.12–0.52, $P<0.01$; $I^2=0\%$; Figure 5).

Dexamethasone Combine 5-HT3 Receptor Antagonist Versus Dexamethasone

Only one trial[22] evaluated PONV in a dexamethasone combined with a 5-HT3 receptor antagonist group and in a dexamethasone alone group. The incidence of POV in the combined group was lower than that in the dexamethasone alone group (5% versus 23%, respectively).

Dexamethasone Dosage

One study[21] compared three different dexamethasone doses with ondansetron. No significant differences were observed between groups in terms of postoperative vomiting on the day of surgery (2/26, 2/27, 2/24) and the following day (1/26, 0/27, 0/24). A similar result was reported in the Madan study (16/42, 15/42, 11/41)[13].

Adverse Effects

Adverse events were described in two trials among dexamethasone groups. Two patients with adverse events were reported in a study by Giannoni et al.[9] One patients went to the emergency room because of pain on the third day after surgery, and the other required hospitalization on the first day after surgery due to nausea and insufficient intake. Subramaniam et al.[15] reported that the probabilities of facial flushing and headache in children receiving dexamethasone were 11.7% and 8.4%, respectively. Madan et al. and Abd-Elshafy et al. [13, 17] showed that there was no significant increase in blood glucose levels in any of the groups.

Discussion

Our meta-analysis showed that dexamethasone reduced the incidence of PONV in children undergoing non-cardiac surgery when administered prophylactically via an intravenous route or via infiltration.

Patients receiving dexamethasone had lower requirement for rescue antiemetics than other patients. Furthermore, the combination of dexamethasone and a 5-HT₃ receptor antagonist was more effective in preventing POV than the 5-HT₃ receptor antagonist or dexamethasone alone.

Recently, a large number of RCTs revealed that various drugs prevent PONV[24, 25]. Dexamethasone has been used as a preoperative preventive antiemetic for quite some time. Karanicolas et al. confirmed that dexamethasone significantly reduced the incidence of PONV after laparoscopic cholecystectomy. In a meta-analysis conducted by Shen et al., dexamethasone and ondansetron were both better than placebo at preventing PONV in children undergoing ophthalmic surgery.

Chu et al. believe that dexamethasone acts as an antiemetic primarily by acting on neurokinin-1 receptors in the central nervous system (CNS) [26]. Dexamethasone enhanced the antiemetic effect of a 5-HT₃ receptor antagonist by activating glucocorticoid receptors as well as serving as a noncompetitive antagonist to 5-HT₃ receptors [27, 28].

There were few complications and adverse events following treatment with dexamethasone. Two RCTs[13, 17] confirmed that postoperative blood glucose levels were not significantly greater in patients treated with dexamethasone than those in patients treated with placebo. Therefore, dexamethasone can be recommended for paediatric non-cardiac surgery.

The included studies showed significant heterogeneity caused by various anaesthetics, doses, types of surgeries and induction techniques. The heterogeneity for most of the results in this study was very small. While evaluating the incidence of PON in the dexamethasone and placebo groups, this result was accompanied by a significant interstudy heterogeneity ($P=0.04$, $I^2=64\%$). We found the heterogeneity was caused by one study[15] after sensitivity analysis. After the study was excluded and the analysis was repeated, the RR was determined to be 0.52, and sensitivity analysis identified a 95% CI of 0.35 to 0.78 ($I^2=5\%$). Therefore, we suggest that dexamethasone can reduce the incidence of PON in children.

Several limitations in the current study should be acknowledged. First, only studies published in English were included in our meta-analysis. Second, the number of studies and the combined sample size were relatively small. As a result, our study may be subject to small study effect bias. Third, some of the studies did not mention methods of blinding, allocation concealment or methods of randomization, possibly resulting in selection bias and performance bias. Fourth, some trials used propofol for induction, which might have antiemetic effects.

Conclusions

In summary, perioperative dexamethasone was an effective measure with few complication for the prevention of PONV in children after non-cardiac surgery.

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Tables

Table1. Details of included studies

| Studies | Age (yr) | Sample size (n) | Type of surgery | Interventions mg*kg ⁻¹ | Anesthetic techniques |
|-----------------|----------|-----------------|---------------------------------|---|---|
| Abd-Elshafy2016 | 2-12 | 90 | Lower limb orthopedic surgery | D 0.5 IV vs D 0.1caudal epidural vs placebo IV | Induction: sevoflurane +fentanyl 2 µ/kg Maintenance: sevoflurane + cisatracurium (0.05mg/kg/dose) |
| Bhardwaj2004 | 2-12 | 100 | Strabismus surgery | D 0.2 IV+ O 0.15 IV vs O 0.15 IV vs placebo IV | Induction: thiopental (4mg/kg) Maintenance: halothane (0.5-1%) + N ₂ O (67%) |
| Celiker2004 | 2-12 | 102 | Tonsillectomy denotonsillectomy | D 0.15 + O 0.05 IV vs D 0.1 + O 0.05 IV vs D 0.05 + O 0.05 IV | Induction: sevoflurane+ N ₂ O Maintenance: sevoflurane (2 %) + N ₂ O (70%) |
| Frelich2018 | 3-9 | 118 | Endoscopic adenoidectomy | D 0.15 IV vs placebo IV | Induction: sevoflurane(8%) Maintenance: sevoflurane for (MAC) value of 1.2-1.5 |
| Gao2015 | 5-10 | 235 | Tonsillectomy | D 0.5 IV vs D 0.5 INF vs placebo IV and INF | Induction: propofol (2 mg/kg) +atracurium (0.4 mg/kg) +fentanyl (4µg/kg) Maintenance: sevoflurane (1.5%) + remifentanyl (0.17µg/kg*min) |
| Giannoni2002 | 3-15 | 50 | Tonsillectomy | D 1.0 IV vs placebo IV | Induction: standard general inhalational anesthetic Maintenance: fentanyl (1 µg/kg) + ropivacaine (1%) + clonidine (1 µg/kg) |
| Gombar2007 | 3-12 | 90 | Middle ear surgery | D 0.15 + G 0.04 IV vs G 0.04 IV vs placebo IV | Induction: thiopentone sodium(4-6mg/kg) + glycopyrrolate (0.01 mg/kg) + morphine (0.15 mg/kg) Maintenance: Halothane(0.51%) + N ₂ O (66%) |
| Madan2005 | 2-15 | 168 | Strabismus surgery | D 0.25 IV vs D 0.5 IV vs D 1.0 IV vs placebo IV | Induction: halothane + N ₂ O or thiopentone Maintenance: halothane (0.5%) + N ₂ O (66%) + vecuronium |
| Montazeri2009 | 3-15 | 62 | Tonsillectomy | D 0.5 INF vs placebo INF | Induction: fentanyl (1-2µg/kg) + thiopental (5 mg/kg) Maintenance: halothane (1.0%) + N ₂ O (50%) |
| Riad2007 | 4-12 | 100 | Strabismus surgery | D 0.5 + M 0.05 IV vs D 0.5 IV vs M 0.05 IV vs placebo IV | Induction: sevoflurane + N ₂ O Maintenance: sevoflurane (0.5-3.0%) + N ₂ O (70%) |

| | | | | | |
|-----------------|------|-----|--------------------|---|---|
| Splinter1998 | 2-14 | 197 | Strabismus surgery | D 0.15 + O 0.05 IV vs placebo + O 0.15 IV |) Induction: propofol (2.5-3.5mg/kg) + lidocain or halothane + N ₂ O Maintenance: halothane (0.75-2.0%) + N ₂ O (70%) |
| Splinter2001 | 2-14 | 193 | Strabismus surgery | D 0.15 + O 0.05 IV vs D 0.15 + placebo IV | Induction: propofol (2.5-3.5mg/kg) + lidocain or halothane + N ₂ O Maintenance: halothane (0.75-2.0%) + N ₂ O (70%) |
| Subramaniam2001 | 2-15 | 135 | Strabismus repair | D 1.0 IV vs O 0.1 IV vs placebo IV | Induction: halothane + N ₂ O or thiopentone Maintenance: halothane + N ₂ O + memperdine (0.5mg/kg) |
| Topal2017 | 3-13 | 60 | Tonsillectomy | D 0.3 INF vs T 0.1 INF vs placebo INF | Induction: thiopental (3-5 mg/kg) + fentanyl (1mg/kg) Maintenance: sevoflurane (2%) + N ₂ O(55%) |

Abbreviations: D, dexamethasone; O, ondansetron; G, granisetron; M, midazolam; T, tramadol; INF, local infiltration

Figures

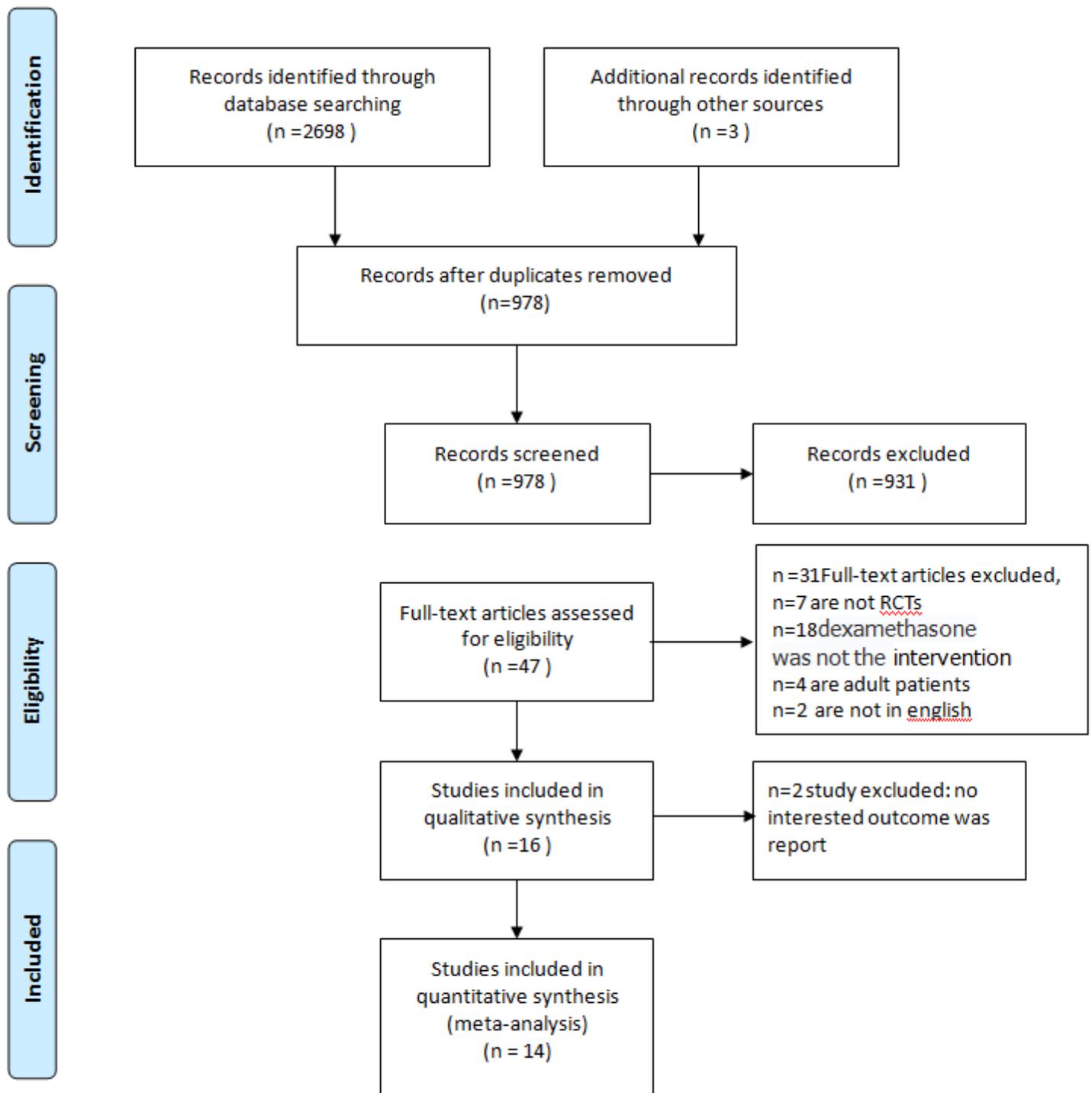


Figure 1

PRISMA flow diagram of the search selection procedure.

| | 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) | Selective reporting (reporting bias) | Other bias |
|-----------------|---|---|---|---|--|--------------------------------------|------------|
| Abd-Elshafy2016 | + | + | + | + | + | + | + |
| Bhardwaj2004 | + | + | ? | + | + | + | + |
| Celiker2004 | + | ? | + | + | + | + | + |
| Frelich2018 | + | + | + | + | + | + | + |
| Gao2015 | + | ? | - | + | + | + | + |
| Giannoni2002 | + | + | + | + | + | + | + |
| Gombar2007 | + | ? | + | + | + | + | + |
| Madan2005 | + | ? | + | + | + | + | + |
| Montazeri2009 | + | + | + | + | + | + | + |
| Riad2007 | + | + | + | + | + | + | + |
| Splinter1998 | + | ? | ? | + | + | + | + |
| Splinter2001 | ? | ? | ? | + | + | + | + |
| Subramaniam2001 | + | + | + | + | + | + | + |
| Topal2017 | ? | ? | + | + | + | + | + |

Figure 2

Quality of assessment of each included studies.

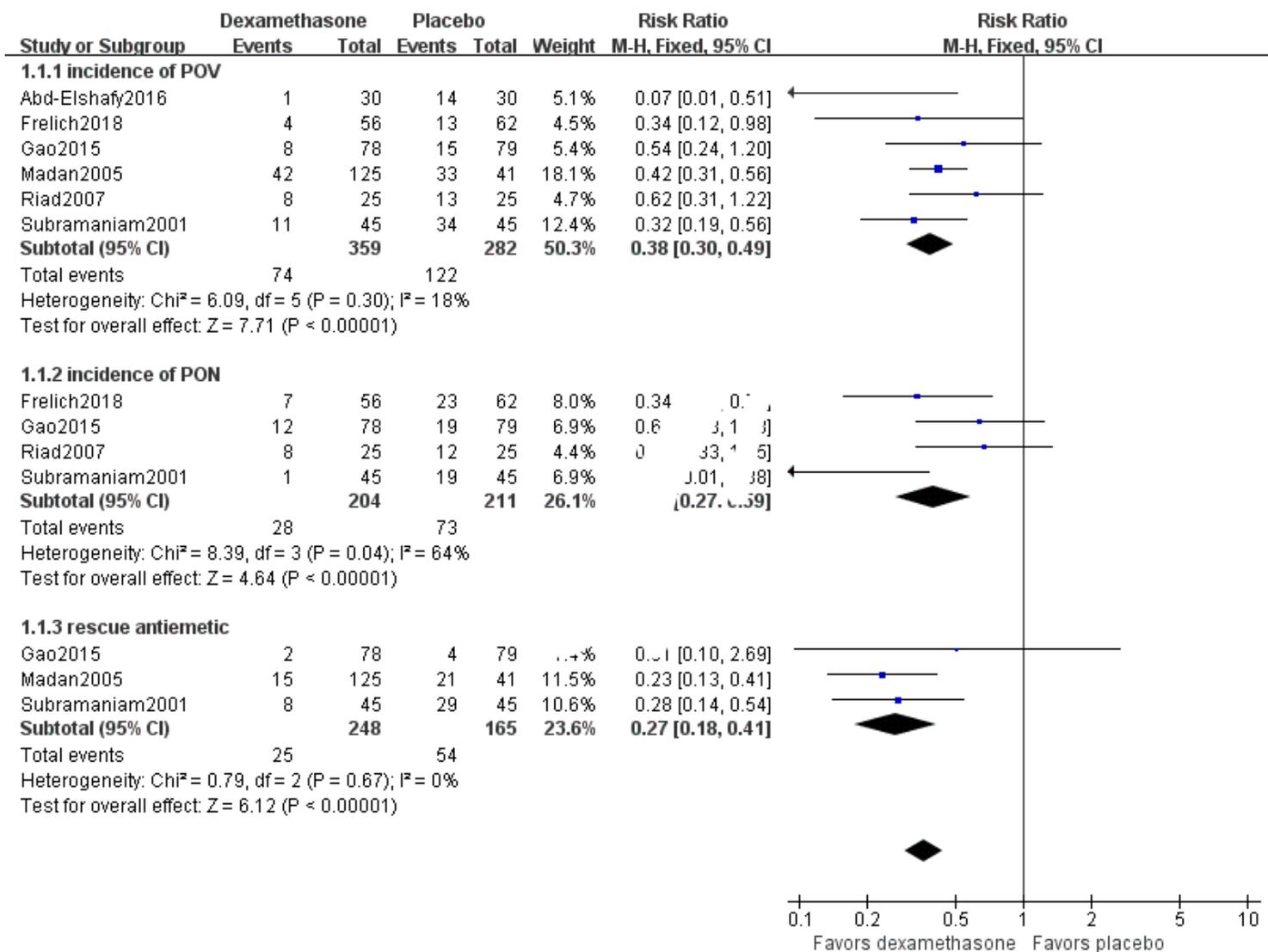


Figure 3

Forest plot of comparison: dexamethason vs placebo. Outcome: 1.1.1 incidence of POV; 1.1.2 incidence of PON ;1.1.3 requirement for rescue antiemetic.

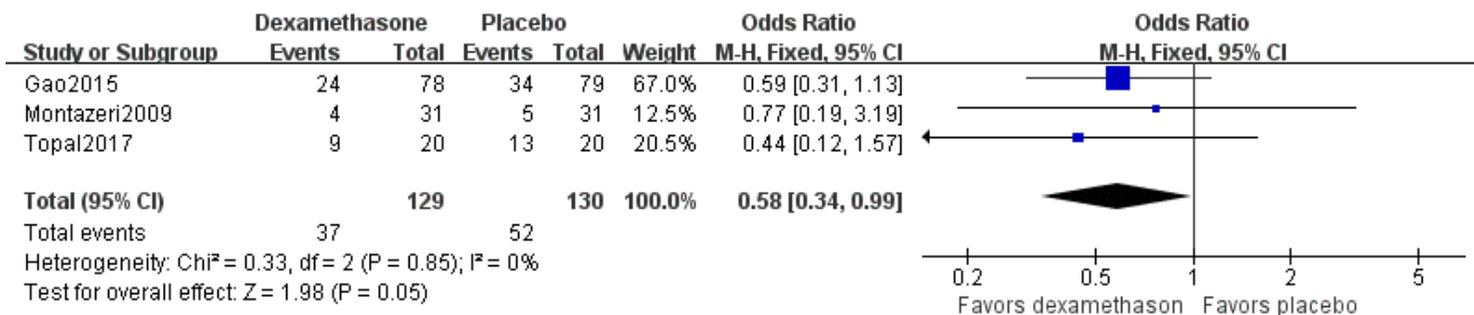


Figure 4

Forest plot of pooled analysis showing incidence of PONV(dexamethason vs placebo by local infiltration).

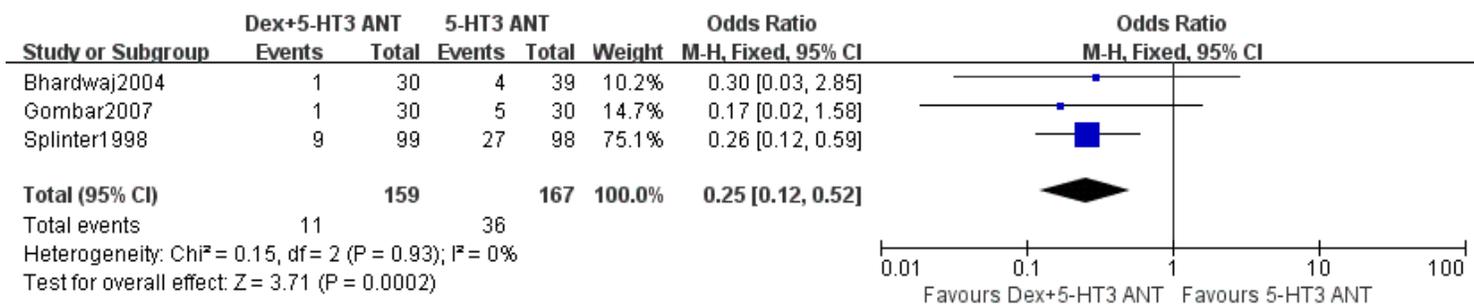


Figure 5

Forest plot of pooled analysis showing incidence of PONV(5-HT3 receptor antagonist and dexamethasone combination versus 5-HT3 receptor antagonist alone).

Supplementary Files

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