Systemic metoclopramide to prevent postoperative nausea and vomiting: a meta-analysis without Fujii's studies

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Editor's key points

- Previous evidence of ineffectiveness of metoclopramide in preventing postoperative nausea and vomiting (PONV) included studies co-authored by Yoshitaka Fujii.
- Recently, the credibility of data from Fujii's studies has been seriously questioned.
- In this meta-analysis, the authors have re-analysed data after excluding the data from Fujii's studies.
- Importantly, the authors have consolidated evidence showing the effectiveness of metoclopramide in treating PONV.

Summary. Previous evidence suggested that 10 mg systemic metoclopramide is not effective to prevent postoperative nausea and/or vomiting (PONV) in patients receiving general anaesthesia. However, the evidence included data with **questioned** validity by the author Yoshitaka Fujii. The objective of the current study was to examine the effect of a systemic dose of 10 mg metoclopramide to prevent PONV.

This quantitative systematic review was performed according to the PRISMA guidelines. A wide search was performed to identify randomized clinical trials that evaluated systemic 10 mg metoclopramide as a prophylatic agent to reduce PONV. Meta-analysis was performed using a random-effect model.

Thirty trials evaluating the effect of 10 mg systemic metoclopramide in 3328 subjects on PONV outcomes were included. Metoclopramide reduced the incidence of 24 h PONV compared with control, odds ratio (OR) [95% confidence interval (CI)] of 0.58 (0.43–0.78), number needed to treat (NNT)=7.8. When evaluated as separate outcomes, metoclopramide also decreased the incidence of nausea over 24 h, OR (95% CI) of 0.51 (0.38–0.68), NNT=7.1, and vomiting over 24 h, OR (95% CI) of 0.51 (0.40–0.66), NNT=8.3. A *post hoc* analysis examining three studies with questioned validity performed by the author Yoshitaka Fujii that would meet criteria for inclusion in the current study did not demonstrate a significant benefit of metoclopramide compared with control on the incidence of 24 h PONV. Our findings suggest that metoclopramide 10 mg i.v. is effective to prevent PONV in patients having surgical procedures under general anaesthesia. Metoclopramide seems to be a reasonable agent to prevent PONV.

Keywords: anaesthesia, general; PONV; premedication, metoclopramide

Postoperative nausea and/or vomiting (PONV) can affect up to 80% of patients undergoing surgical procedures.¹ Clinically significant PONV can substantially decrease patient's quality of postsurgical recovery and result in serious consequences to patient's health including dehydration with electrolyte disturbance, bleeding, and oesophageal laceration.² ³ Drug shortages around the world have recently limited the access to commonly used medications to prevent PONV such as ondansetron and dexamethasone.⁴

Metoclopramide is a safe and inexpensive medication that has been used to prevent PONV worldwide. A previous systematic review did not find a clinically meaningful effect of 10 mg systemic metoclopramide to prevent PONV.⁵ The current Society of Ambulatory Anaesthesia guidelines to prevent PONV do not recommend metoclopramide as an efficacious agent to prevent PONV.⁶ It is important to note that much of the evidence for the lack of efficacy of metoclopramide included studies with questioned validity originated by the author Yoshitaka Fujii.⁷ It has been recently recommended that systematic reviews should exclude data originated from Yoshitaka Fujii.⁸ Therefore, it remains unknown if a common 10 mg dose of systemic metoclopramide is efficacious to prevent PONV.

The main objective of the current investigation was to evaluate the effect of systemic metoclopramide in the prevention of PONV. A secondary objective was to examine if the effect of metoclopramide in the prevention of PONV changed when the medication was administered as a single agent or as part of a combination therapy.

Methods

This quantitative systematic review was conducted following the guidelines of the PRISMA statement. $^{\rm 9}$

Systematic search

Published reports of randomized trials evaluating the effects of metoclopramide on surgical PONV were searched using the National Library of Medicine's Pubmed database, Embase, the Cochrane Database of Systematic Reviews and Google Scholar inclusive to March 1, 2012. Free text and MeSH terms 'metoclopramide', 'nausea', 'vomiting', and 'postoperative' were used individually and in various combinations. No language restriction was used. The search was limited to randomized controlled clinical trials in subjects older than 18 yr of age. An attempt to identify additional studies not found by the primary search methods was made by reviewing the reference lists from identified studies. No search was performed for unpublished studies. This initial search yielded 159 randomized clinical trials.

Selection of included studies

The study's inclusion and exclusion criteria were determined before the systematic search. Two authors (G.S.D.O. and L.J.C.-A. or R.C.) independently evaluated the abstract and results of the 159 articles obtained by the initial search. Articles that were clearly not relevant based on our inclusion and exclusion criteria were excluded at this phase. Disagreements on inclusion of the articles were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute was resolved with the help of a fourth investigator (E.Y.).

Inclusion and exclusion criteria

We included randomized controlled trials of a single perioperative 10 mg i.v. metoclopramide administration with an inactive (placebo or 'no treatment') control group. Excluded were trials reporting nausea and vomiting after emergency medicine and non-surgical patients. Trials evaluating multiple perioperative metoclopramide doses or that evaluated metoclopramide to treat PONV were excluded to maximize clinical homogeneity. Studies containing a concurrent use of an alternative multimodal anti-emetic regimen were excluded if a direct comparison of metoclopramide and placebo could not be established. Included studies had to report at least on the incidence of early (1-6 h) or 24 h PONV. No minimum sample size was required for inclusion in the meta-analysis. The studies performed by the author Yoshitaka Fujii were excluded, as recently recommended, due to the questioned validity of the data originated in those studies (Fig. 1).^{7 8}

Validity scoring

Two authors (G.S.D.O. and L.J.C.-A. or R.C.) independently read the included reports and assessed their methodological validity using a modified Jadad five-point quality scale.¹⁰ The scale evaluates the study for the following: randomization, double-blind evaluation, concealment of study group to evaluator, valid randomization method, and completeness of data at follow-up. Discrepancies in rating of the trials were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute was resolved with the help of a fourth investigator (E.Y.). As only randomized trials were included in the analysis, the minimum possible score of an included trial was 1 and the maximum was 5. Trials were not excluded or weighted in the analysis based on quality assessment scores.

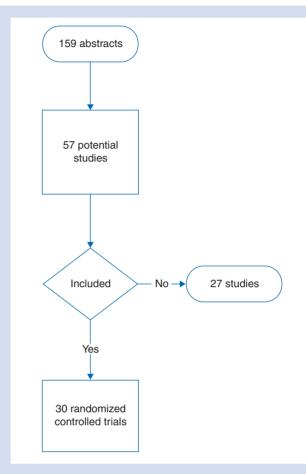


Fig 1 Flow chart outlining retrieved, excluded, and evaluated randomized controlled trials.

Data extraction

Two authors (G.S.D.O. and L.J.C.-A. or R.C.) independently evaluated the full manuscripts of all included trials and performed data extraction using a data collection form specifically developed for this review. Discrepancies were resolved by discussion between the two investigators. If an agreement could not be reached between two investigators, the decision was made by a fourth investigator (E.Y.). Data extracted from trials included metoclopramide dose and time of administration, sample size, number of subjects in treatment groups, follow-up period, type of surgery, nausea and/or vomiting over 24 h, early nausea and/or vomiting (1-6 h), need for rescue anti-emetic, type of drug intervention (single regimen vs combination therapy), and adverse events.

Data were initially extracted from tables or text. For data not available in tables, attempts to contact authors were made; if the authors did not respond or did not have current contact information, the data were abstracted from available figures. Dichotomous data on the presence or absence of adverse effects were extracted and converted to incidence.

Definition of relevant outcome data

Primary outcomes

Twenty-four hour incidence of PONV (defined as nausea and/ or vomiting), early (up to 6 h after operation) incidence of PONV, early and 24 h incidence of nausea, and early and 24 h incidence of vomiting (including retching) were the primary outcomes.

Secondary outcomes

These were the need for rescue anti-emetic, and adverse events including headache, dizziness, postoperative sedation, and extrapyramidal symptoms.

Meta-analyses

For dichotomous data, odds ratio (OR) and 95% confidence interval (CI) are reported. For dichotomous adverse effects data, the Peto OR (to account for the potential of zero counts in the cells for low-frequency outcomes) and 95% CI are reported. For a significant effect compared with placebo required for dichotomous data, the confidence interval did not include 1.0. We calculated the number needed to treat (NNT), based on the absolute risk reduction, as an estimate of a beneficial effect. Owing to the different surgical procedures, a random-effect model was used in an attempt to generalize our findings to studies not included in our meta-analysis.¹¹ Publication bias was evaluated by examining for the asymmetry of funnel plots using Egger's regression test.¹² A one-sided P<0.05 was considered as an indication of an asymmetric funnel plot. A file drawer analysis described by Rosenthal¹³ was performed in the case of an asymmetric funnel plot. The test estimates the lowest number of additional studies that if they became available would reduce the combined effect to non-significance, assuming that the average Z-score of the combined P-values of these missing studies would be 0. A separate post hoc analysis of the studies performed by the author Yoshitaka Fujii that would meet criteria for inclusion in the current analysis was also performed.

Heterogeneity of the included studies was considered to be present if the I^2 statistic was >30%. Further analysis was planned *a priori* to explore relevant heterogeneity. Subgroup analysis was performed to investigate the effect of type of anti-emetic intervention (single therapy vs combination therapy). A Q statistic was used to compare the effects between subgroups. The proportion of the total variance explained by the covariates (R^2) was calculated by dividing random effects pooled estimates of variance (tau-squared) within studies by total variance (total tau-squared). The value obtained was then subtracted from 1. When values decrease outside the range of 0–100%, they were set to the closest value (0% or 100%).

Analysis was performed using Stata version 11 (College Station, TX, USA) and Comprehensive Meta-analysis software version 2 (Biostat, Englewood, NJ, USA).

Results

Of the 159 initially evaluated abstracts, 57 studies initially met the inclusion criteria. Twenty-seven studies were subsequently excluded: seventeen did not provide a direct comparison between metoclopramide and placebo or did not report the evaluated outcomes,¹⁴⁻³⁰ five evaluated weightbased responses of the evaluated outcomes,31-35 two examined patients undergoing regional anaesthesia,^{36 37} two were retracted, (Piper SN, Suttner SW, Röhm KD, Maleck WH, Larbig E, Boldt J. Dolasetron, but not metoclopramide prevents nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Can J Anaesth 2002; 49: 1021-8 and Abou Zeid H, Al-Gahamdi A, Abdul-Hadi M. Dolasetron decreases postoperative nausea and vomiting after breast surgery. Breast J 2002; 8: 216-21) and one examined metoclopramide administered after operation.³⁸ The characteristics of included studies are listed in Supplementary Table S1. The evaluated trials included data from 3328 subjects and were published between 1967 and 2011.39-68 The median number of patients in the included studies receiving metoclopramide was 36.5. The median modified Jadad scale score was 4. The trials tested a single dose of 10 mg i.v. metoclopramide given either before operation or intraoperatively in a large variety of surgical procedures under general anaesthesia. All 30 studies included reported on nausea and/ or vomiting.

Twenty-four hours nausea and/or vomiting (PONV)

The aggregated effect of 13 studies (14 comparisons)³⁹⁻⁶⁷ examining the effect of 10 mg systemic metoclopramide on the 24 h incidence of nausea and/or vomiting compared with placebo showed a beneficial effect of metoclopramide, OR (95% CI) of 0.58 (0.43–0.78), NNT=7.8. The funnel plot did not demonstrate asymmetry (P=0.38). Heterogeneity was low (I^2 =0) (Fig. 2).

Only one study ⁴⁴ examined metoclopramide used as a combination therapy, but it did not achieve a significant benefit compared with placebo, OR (95% CI) of 0.49 (0.14-1.62).

The combined effect of three studies⁶⁹⁻⁷¹ performed by the author Yoshitaka Fujii that would meet inclusion criteria in the current meta-analysis did not show a significant beneficial effect of 10 mg i.v. metoclopramide compared with placebo on the incidence of 24 h PONV, OR (95% CI) of 0.72 (0.39–1.31).

Early (1-6 h) nausea and/or vomiting

The overall effect of 11 studies (12 comparisons)^{41 44 45 47 49 62 63 65-68} examining 10 mg i.v. metoclopramide on the incidence of early nausea and/or vomiting compared with placebo favoured metoclopramide, OR (95% CI) of 0.52 (0.36-0.75), NNT=7.6 (Fig. 3). The funnel plot did not demonstrate asymmetry (P=0.08). Heterogeneity was low (I^2 =24).

The only study examining the effect of metoclopramide used in a combination regimen on the incidence of early

| Study name | Comparison Outcome | | Statistics for each study | | | | | Events/Total | | | Odds ratio and 95% Cl | | | |
|-----------------|--------------------|----------|---------------------------|----------------|-------|---------|---------|----------------|-----------|------|-----------------------|----------|---------|-----|
| | | | Odds ratio | Lower limit | | Z-value | P-value | Metoclopramide | Control | | | | | |
| Ekinci | Meto-saline | PONV 24h | 0.441 | 0.123 | 1.573 | -1.262 | 0.207 | 9 / 20 | 13/20 | | I— | | | |
| Kaki | Meto-saline | PONV 24h | 1.000 | 0.291 | 3.437 | 0.000 | 1.000 | 7 / 25 | 7/25 | | | • | | |
| Nasek-adam | Meto-saline | PONV 24h | 0.545 | 0.224 | 1.325 | -1.338 | 0.181 | 18 / 40 | 24 / 40 | | - | | | |
| Nasek-adam 2 | Meto-saline | PONV 24h | 0.492 | 0.149 | 1.626 | -1.163 | 0.245 | 5 / 40 | 9/40 | | | | | |
| Nasek-adam 2004 | Meto-saline | PONV 24h | 0.632 | 0.246 | 1.623 | -0.954 | 0.340 | 15 / 35 | 19/35 | | - | | | |
| Huang | Meto-saline | PONV 24h | 0.648 | 0.259 | 1.621 | -0.927 | 0.354 | 20 / 38 | 24/38 | | - | | | |
| Nuhammad | Meto-saline | PONV 24h | 0.818 | 0.208 | 3.216 | -0.287 | 0.774 | 9 / 16 | 11/16 | | - | | | |
| Sharma | Meto-saline | PONV 24h | 0.844 | 0.270 | 2.644 | -0.291 | 0.771 | 13 / 24 | 14/24 | | - | _ | | |
| Rusch 1999 | Meto-saline | PONV 24h | 0.254 | 0.090 | 0.720 | -2.580 | 0.010 | 13 / 33 | 23/33 | | | | | |
| Pertusa | Meto-saline | PONV 24h | 0.260 | 0.073 | 0.921 | -2.088 | 0.037 | 9 / 22 | 16/22 | | | | | |
| Vaguib | Meto-saline | PONV 24h | 0.925 | 0.279 | 3.069 | -0.127 | 0.899 | 17 / 24 | 21/24 | | - | _ | | |
| Desilva | Meto-saline | PONV 24h | 0.758 | 0.365 | 1.574 | -0.744 | 0.457 | 29 / 58 | 33 / 58 | | | _ | | |
| Bone | Meto-saline | PONV 24h | 0.429 | 0.117 | 1.568 | -1.280 | 0.201 | 10 / 20 | 14/20 | | | | | |
| Naldmann | Meto-saline | PONV 24h | 0.619 | 0.158 | 2.429 | -0.688 | 0.492 | 5 / 20 | 7/20 | | — — | | | |
| | | | 0.585 | 0.439 | 0.780 | -3.652 | 0.000 | 179 / 415 | 235 / 421 | | | | | |
| | | | | | | | | | | 0.01 | 0.1 | 1 | 10 | 100 |
| | | | | | | | | | | | Metoclopramide | | Control | |

Fig 2 Pooled data evaluating the effect of systemic metoclopramide on the 24 h incidence of PONV compared with control. Data were evaluated by calculating OR. The point estimate (95% CI) for the overall effect was 0.58 (0.43–0.78). OR for individual studies represented by the square on the Forrest plot with 95% CI of the difference shown as a solid line. Larger sized squares denote larger sample size. The diamond represents the pooled estimate and uncertainty for the combined effect.

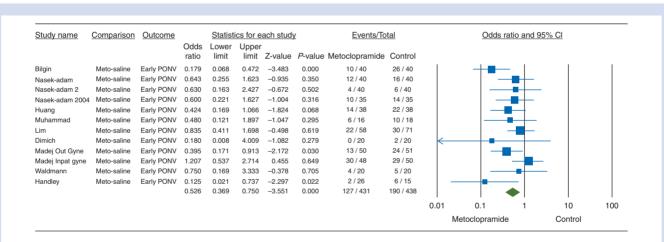


Fig 3 Pooled data evaluating the effect of systemic metoclopramide on the early incidence of PONV compared with control. Data were evaluated by calculating OR. The point estimate (95% CI) for the overall effect was 0.52 (0.36–0.75). OR for individual studies represented by the square on the Forrest plot with 95% CI of the difference shown as a solid line. Larger sized squares denote larger sample size. The diamond represents the pooled estimate and uncertainty for the combined effect.

 $PONV^{44}$ did not demonstrate a significant benefit, OR (95% CI) of 0.63 (0.16–2.42).

Twenty-four hour incidence of nausea

The combined effect of 10 studies (11 comparisons)^{40 44 46 47} $^{51-53}$ 55 59 60 examining the effect of 10 mg i.v. metoclopramide on the incidence of 24 h nausea compared with placebo favoured metoclopramide, OR (95% CI) of 0.51 (0.38–0.68), NNT=7.1 (Fig. 4). Heterogeneity was low (I^2 =8). The funnel plot demonstrated some asymmetry, indicating the possibility of publication bias (P=0.03). Rosenthal analysis estimated that 92 missing studies would be required to change the analysis.

The only study examining the effect of metoclopramide used in a combination therapy on the incidence of 24 h nausea⁴⁰ did not show a significant benefit, OR (95% CI) of 0.34 (0.06-1.99).

The combined effect of three studies⁶⁹⁻⁷¹ performed by the author Yoshitaka Fujii that would meet inclusion criteria in the current meta-analysis did not show a significant beneficial effect of 10 mg i.v. metoclopramide compared with placebo on the incidence of nausea over 24 h, OR (95% CI) of 0.76 (0.36–1.57).

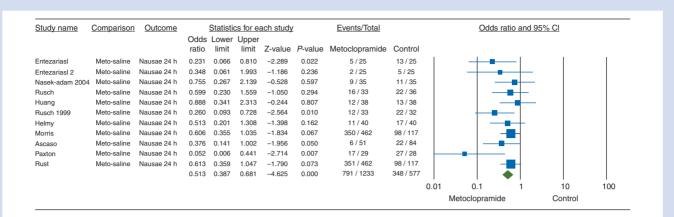


Fig 4 Pooled data evaluating the effect of systemic metoclopramide on the 24 h incidence of nausea compared with control. Data were evaluated by calculating OR. The point estimate (95% CI) for the overall effect was 0.51 (0.38–0.68). OR for individual studies represented by the square on the Forrest plot with 95% CI of the difference shown as a solid line. Larger sized squares denote larger sample size. The diamond represents the pooled estimate and uncertainty for the combined effect.

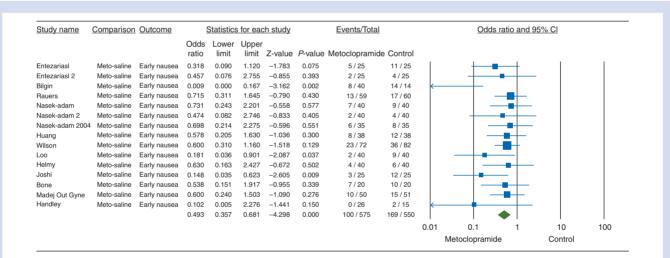


Fig 5 Pooled data evaluating the effect of systemic metoclopramide on the early incidence of nausea compared with control. Data were evaluated by calculating OR. The point estimate (95% CI) for the overall effect was 0.49 (0.35–0.68). OR for individual studies represented by the square on the Forrest plot with 95% CI of the difference shown as a solid line. Larger sized squares denote larger sample size. The diamond represents the pooled estimate and uncertainty for the combined effect.

Early (1-6 h) incidence of nausea

The aggregated effect of 13 studies (14 comparisons)^{40-45 47} ^{48 52 54 61 64 65 68} evaluating 10 mg i.v. metoclopramide on the incidence of early nausea compared with placebo favoured metoclopramide, OR (95% CI) of 0.49 (0.35–0.68), NNT=5.9 (Fig. 5). Heterogeneity was low (I^2 =7). The funnel plot demonstrated asymmetry, suggesting the possibility of publication bias (*P*=0.001). Eighty-nine missing studies would be required in order to change the analysis.

The combined effect of three studies⁴⁰ ⁴⁴ ⁵⁴ evaluating the effect of 10 mg i.v. metoclopramide as part of a combination therapy on the incidence of early nausea suggested a benefit of metoclopramide compared with placebo, OR (95% CI) of 0.32 (0.12–0.87), NNT=10.6. Heterogeneity was low (I^2 =0). Funnel plot did not demonstrate asymmetry (P=0.35).

Vomiting over 24 h

The aggregated effect of 10 studies (11 comparisons)^{40 45-47} $^{51-53}$ 55 59 60 evaluating metoclopramide on the incidence of vomiting over 24 h demonstrated a beneficial effect of metoclopramide, OR (95% CI) of 0.51 (0.40–0.66), NNT=8.3 (Fig. 6). Heterogeneity was low (I^2 =0). The funnel plot did not demonstrate asymmetry (P=0.07).

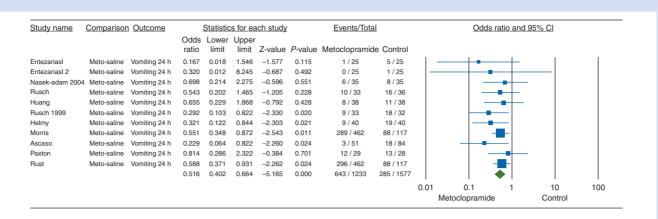


Fig 6 Pooled data evaluating the effect of systemic metoclopramide on the 24 h incidence of vomiting compared with control. Data were evaluated by calculating OR. The point estimate (95% CI) for the overall effect was 0.51 (0.40–0.66). OR for individual studies represented by the square on the Forrest plot with 95% CI of the difference shown as a solid line. Larger sized squares denote larger sample size. The diamond represents the pooled estimate and uncertainty for the combined effect.

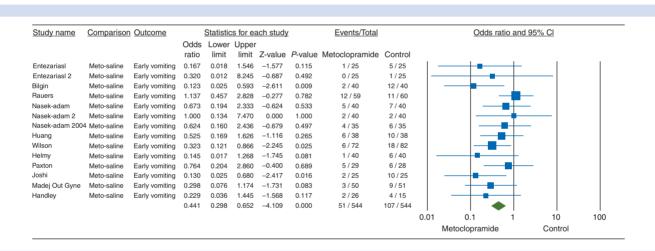


Fig 7 Pooled data evaluating the effect of systemic metoclopramide on the early incidence of vomiting compared with control. Data were evaluated by calculating OR. The point estimate (95% CI) for the overall effect was 0.44 (0.29–0.65). OR for individual studies represented by square on the Forrest plot with 95% CI of the difference shown as solid line. Larger sized squares denote larger sample size. The diamond represents the pooled estimate and uncertainty for the combined effect.

The only study evaluating the effect of metoclopramide when used as part of a combination therapy⁴⁰ did not show a significant effect on the reduction of vomiting over 24 h, OR (95% CI) of 0.32 (0.01-8.24).

The combined effect of three studies⁶⁹⁻⁷¹ performed by the author Yoshitaka Fujii that would meet inclusion criteria in the current meta-analysis did not show a significant beneficial effect of 10 mg i.v. metoclopramide compared with placebo on the incidence of 24 h vomiting, OR (95% CI) of 0.77 (0.38–1.56).

Early (1-6 h) vomiting

The overall combined effect of 12 studies (14 comparisons) $^{40-42}$ $^{44-48}$ 52 59 61 65 68 evaluating the effect of 10 mg i.v. metoclopramide on the incidence of early vomiting

compared with placebo favoured metoclopramide, OR (95% CI) of 0.44 (0.29–0.65), NNT=10.5 (Fig. 7). Heterogeneity was low (I^2 =5). The analysis was limited by the presence of an asymmetric funnel plot (P=0.03), suggesting the presence of publication bias. Sixty-three missing studies would be required to change the analysis.

The combined effect of two studies^{40 44} evaluating metoclopramide as part of a combination regimen did not show a significant benefit compared with control, OR (95% CI) of 0.72 (0.13-4.03).

Postoperative need for rescue anti-emetics in 24 h

The aggregate effect of three studies^{46 49 51} examining 10 mg i.v. metoclopramide on the need of rescue anti-emetics over 24 h demonstrated a beneficial effect of

metoclopramide compared with placebo, OR (95% CI) of 0.41 (0.19–0.92), NNT=6.0. Heterogeneity was low (I^2 =0). The funnel plot was not asymmetric (P=0.31). All three studies evaluated metoclopramide as a single agent for PONV prophylaxis.

Safety analysis

Extrapyramidal symptoms

Two studies reported the presence of extrapyramidal symptoms.⁶⁵ ⁶⁶ The combined effect did not show a significant effect of metoclopramide, OR (95% CI) of 1.0 (0.2–3.7). Heterogeneity was low ($I^2=0$).

Dizziness

The combined effect of five studies^{39 41 44 45 53} did not reveal a significant effect of metoclopramide on the incidence of postoperative dizziness, OR (95% CI) of 1.3 (0.5–3.5). Heterogeneity was low ($I^2=0$).

Headache

The overall effect of six studies on the incidence of postoperative headache^{39 41 44 45 53 56} did not reveal a significant effect of metoclopramide over placebo, OR (95% CI) of 0.7 (0.4–1.4). Heterogeneity was low ($I^2=0$).

Sedation

The aggregated effect of eight studies³⁹ ⁴¹ ⁴⁴ ⁴⁵ ⁵⁰ ⁶² ⁶⁵ ⁶⁶ examining the effect of metoclopramide on postoperative sedation did not show a significant effect of metoclopramide, OR (95% CI) of 1.0 (0.6–1.5). Heterogeneity was low (I^2 =0).

Discussion

The most important finding of the current investigation is the detection of an effect of systemic metoclopramide in the prevention of PONV. Metoclopramide was also effective in reducing the incidence of nausea and vomiting when these outcomes were examined **separately**. Systemic metoclopramide can also be a viable alternative to **prevent PONV** in countries where other anti-emetic agents are cost prohibitive.⁷²

Our findings have important clinical implications because a **previous** systematic review examining the effect of metoclopramide did **not find** a clinically significant effect in the reduction in PONV.⁵ It is important to note that the previous systematic review included multiple trials with **questioned** validity performed by the author Yoshitaka Fujii.⁷ [§] This trials were performed to compare 'newer' anti-emetic agents with saline and metoclopramide and did not demonstrate a benefit of metoclopramide compared with saline, as demonstrated in our *post hoc* analysis. Expert reviews and the current Society of Ambulatory Anaesthesia guidelines do not recommend systemic metoclopramide to prevent PONV.⁶ ⁷³ ⁷⁴ Our results suggest that metoclopramide is a reasonable alternative to other commonly used anti-emetic.

It remains to be determined if the 10 mg i.v. metoclopramide offers benefit when used as a second anti-emetic as part of a multimodal therapy. Our analysis was very limited by the low number of studies providing that comparison. Wallenborn and colleagues³⁶ have performed a large randomized controlled trial where they found a benefit of greater doses of metoclopramide (25 and 50 mg) but not 10 mg i.v. in combination with dexamethasone to prevent PONV. We excluded that trial from our analysis because the anaesthetic care was not standardized and some subjects received regional anaesthesia. Recently, Mishriky and Habib⁷⁵ found a benefit of 10 mg i.v. metoclopramide to prevent PONV in patients undergoing Caesarean delivery under regional anaesthesia, but their analysis did not include subgroup comparisons testing the efficacy of 10 mg i.v. metoclopramide given as part of a combination regimen.

PONV has been mentioned as a frequent reason to prolong hospital discharge.⁷⁶ In the current investigation, we were able to demonstrate a clinically significant effect of 10 mg i.v. metoclopramide in early PONV (NNT=7.6). The clinical effect seems to be more pronounced against nausea (NNT=5.9) than against vomiting (NNT=10.5). It is plausible that the addition of a drug with reported greater anti-vomiting effects than anti-nausea effects such as ondansetron may provide additional benefits on early symptoms of PONV and expedite hospital discharge.⁷⁷ Future studies to examine the effect of metoclopramide on time to hospital discharge are required.

Our systematic review did **not detect** an increase in commonly reported side-effects such as headache, dizziness, or sedation because of the use of systemic 10 mg i.v. metoclopramide. Only two studies reported on the incidence of **extrapyramidal symptoms**, but the combined effect did **not suggest** an increase in those side-effects compared with saline (OR=1.0). Wallenborn and colleagues³⁶ found that greater doses of metoclopramide caused more tachycardia and a small risk of extrapyramidal symptoms. The 10 mg i.v. metoclopramide is clinically effective to reduce PONV and does not seem to have the side-effects reported by greater dosage regimens.

It seems that the clinical effect of metoclopramide when used as a single regimen has similar efficacy as commonly used anti-emetic agents, specifically when examining the previously reported efficacy of those agents. Henzi and colleagues⁷⁸ evaluating the effect of 8–10 mg dexamethasone in a systematic review reported that the NNT (95% CI) to prevent early and late vomiting compared with placebo in adults was 7.1 (95% CI 4.5–18). With regard to ondansetron, the NNT was found to be 6 for the prevention of vomiting and ~7 for the prevention of nausea.⁶ Nevertheless, only a direct comparison will be able to exclude potential benefits of other agents compared with metoclopramide in PONV prophylaxis.

We assessed the risk of bias in the individual studies using the Jadad scale. The use of rating scales is controversial in systematic reviews due to large interobserver variation detected in the utilization of those scales. We attempted to minimize the effect of interobserver variation by having two investigators rate the studies and a third investigator in cases of a dispute. In addition, we did not exclude studies based on rating and did not perform a weighted analysis based on the study quality. It is also important to note that the use of scale does not exclude the possibility of bias in the individual studies.

Our analysis is only valid if interpreted within the context of its limitations. In order to obtain generalizable results, we have included a large number of different surgical procedures which can be criticized when performing quantitative systematic reviews. Nevertheless, the measured heterogeneity in all analysis was very low which in fact suggests the generalizability of our findings. Some of our secondary analysis was limited by the presence of an asymmetric funnel plot and the possibility of publication bias; therefore, those analyses need to be interpreted with caution. It is possible that the detection of studies that were file drawered because of negative results could possibly overestimate the ORs determined in some of those analyses.⁷⁹

In summary, we demonstrated that 10 mg i.v. metoclopramide is effective to prevent PONV in patients having surgical procedures under general anaesthesia. In times of drug shortages and in circumstances where other anti-emetic are cost prohibitive, metoclopramide seems to be a reasonable alternative to prevent PONV.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

None declared.

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