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Review

Drugs for preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: Network meta-analysis of randomized clinical trials and trial sequential analysis

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ABSTRACT

Background: Different categories of drugs are used to reduce the incidence of post-operative nausea and vomiting (PONV) following laparoscopic cholecystectomy (LC). This study is a network meta-analysis of randomized clinical trials with such drugs.

Methods: Electronic databases were searched for appropriate randomized clinical trials evaluating drugs reducing PONV in LC. Number of patients without PONV at 24 h was the primary outcome; and incidence of nausea and/or vomiting at 6 h and 24 h, and adverse events were the secondary outcome measures. Risk of bias was evaluated for each study. Mixed treatment comparison estimates were derived by random-effects modelling. Trial sequential analysis was carried out to assess the adequacy of evidence; and surface area under cumulative ranking curve was generated to identify the best intervention in the pool. Grading of the evidence for key comparisons was done.

Results: Ninety clinical trials were included. Metoclopramide, gabapentin, dixyrazine, ondansetron, granisetron, dexamethasone, tropisetron, droperidol, droperidol/dexamethasone, droperidol/metoclopramide, granisetron/droperidol and granisetron/dexamethasone, haloperidol, dexmedetomidine, palonosetron, droperidol/ondansetron, metoclopramide/dexamethasone, haloperidol/ondansetron, haloperidol/dexamethasone, palonosetron/dexamethasone and ramosetron/dexamethasone were observed with significant benefits compared to placebo. Corticosteroid/serotonin receptor antagonists was observed with the highest probability of being the 'best' in this pool. However, the moderate quality of evidence obtained was adequate to confirm the benefits of dexamethasone and ondansetron only.

Conclusion: The relative effect sizes for various prophylactic anti-emetics for LC was modelled using the principles of network meta-analysis. Dexamethasone and ondansetron have the best evidence as stand-alone options and the combination is preferred in high-risk category. Caution should be exercised while interpreting the evidence as the estimates might change with head-to-head clinical trial data.

1. Introduction

Incidence of post-operative nausea and vomiting (PONV) following surgery under general anaesthesia is around 30% [1]. PONV following laparoscopic cholecystectomy (LC) has been variedly reported to be higher between 45 and 75% [2]. Particularly, the pneumoperitoneum in LC increases the vagal discharge resulting in increased incidence of PONV [3]. PONV may cause discomfort, aspiration of gastric contents, metabolic consequences and prolongation of hospital stay. Females, younger age, history of PONV or motion sickness, non-smoking status and increased duration of surgery are some of the proven risk factors for PONV [4].

Prophylactic interventions in the form of anti-emetics such as serotonin receptor antagonists, corticosteroids, prokinetics and anti-psychotics have been explored in clinical trials to reduce the risk of PONV [5]. Combination of these anti-emetics have also been shown to be effective. Several meta-analyses have been carried out comparing various anti-emetic drug classes with conflicting results [6–11]. However, they were primarily direct comparisons and greatly limited in terms of generalizability and not considered in totality with other interventions. Network meta-analysis offers the advantage of comparing interventions for a particular disease/condition in a single platform [12]. To explain

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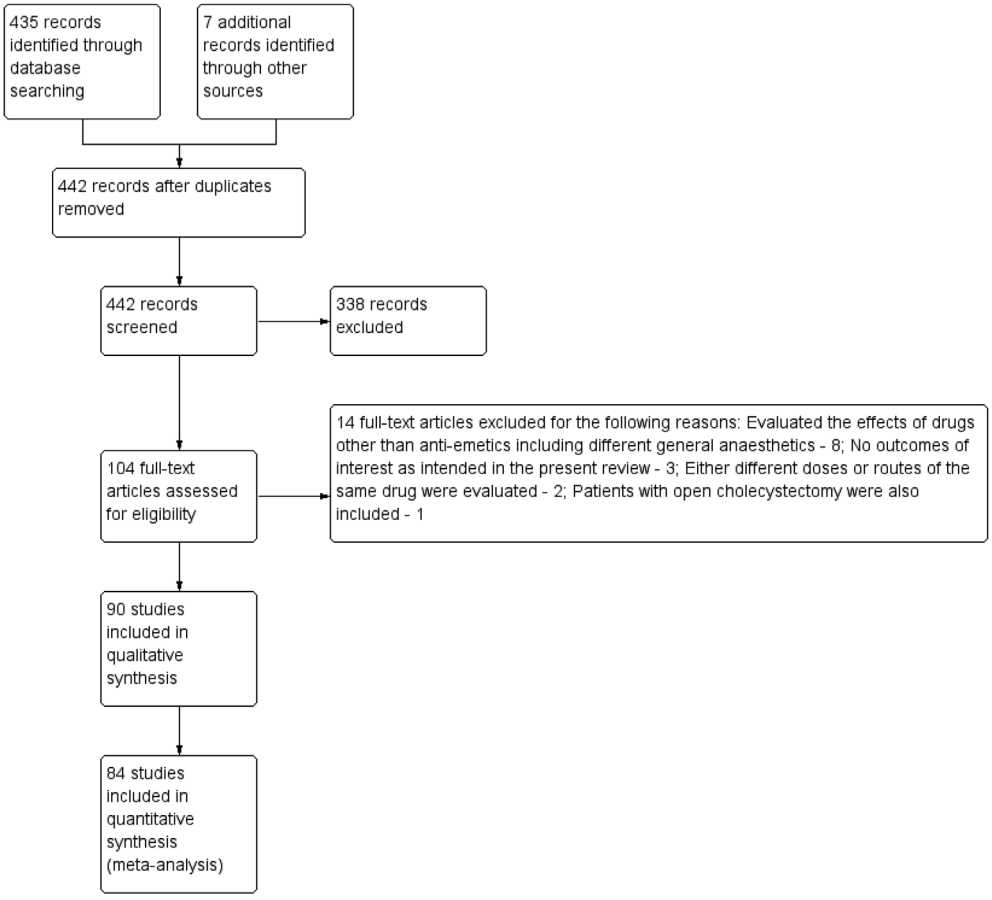


Fig. 1. PRISMA flow diagram.

with an example, let's assume that there are three interventions A, B and C and clinical trials exist comparing A and B; and B and C only. Through the principle of network meta-analysis, pooled effect estimates can be computed between A and C through the common comparator B. Hence, this network meta-analysis was carried out to compare the effects of prophylactic anti-emetic administration in patients undergoing LC.

2. Methods

2.1. Information source and search strategy

The protocol for this review was registered in PROSPERO with the identification number CRD42017072786. The following search strategy: ((metoclopramide [tiab] OR tropisetron [tiab] OR aprepitant [tiab] OR scopolamine [tiab] OR haloperidol [tiab] OR propofol [tiab] OR 5-HT3 [tiab] OR 5-HT [tiab] OR benzodiazepine [tiab] OR diazepam [tiab] OR cannabinoid [tiab] OR cisapride [tiab] OR mozapride [tiab] OR tegaserod [tiab] OR chlorpromazine [tiab] OR prochlorperazine [tiab] OR dolasetron [tiab] OR domperidone [tiab] OR ramosetron [tiab] OR droperidol [tiab] OR dopamine [tiab] OR serotonin [tiab] OR ondansetron [tiab] OR sugammadex [tiab] OR granisetron [tiab] OR palonosetron [tiab] OR dexamethasone [tiab] OR corticosteroid [tiab])) AND ((((laparoscop* [tiab]) AND cholecyst* [tiab])) OR “Cholecystectomy, Laparoscopic" [Majr]) was used in Medline (through PubMed) and Cochrane CENTRAL. No limits were applied for either the publication year or language and the thorough literature search was completed on 24 July 2017. Manual search for potential studies from references in the eligible articles was also carried out.

2.2. Eligibility criteria

Randomized clinical trials conducted in patients undergoing LC where effects of two or more anti-emetics were assessed or compared to placebo, were included. The included studies also evaluated the administration of anti-emetics at the end of surgery for which we carried out a sensitivity analysis. Similarly, we also included studies that have not explicitly stated the prior administration of anti-emetics before recruiting in the study as well as that administered propofol as general anaesthetic agent and separate sensitivity analyses for each were carried out.

2.3. Outcome variables

Complete response as defined by absence of PONV was the primary outcome variable and the secondary outcomes were as follows: Incidence of nausea at 4–6 h and at 24 h; incidence of vomiting at 4–6 h and at 24 h; use of rescue anti-emetics and adverse events.

2.4. Study procedure and statistical analysis

Two authors independently performed the literature search and extracted the following details: trial site, year, trial methods, participants, interventions, and outcomes. Dis-agreement was resolved through discussion. The present network meta-analysis complies with the Assessing the methodological quality of systematic reviews (AMSTAR) and the Preferred Reporting Items in Systematic review and Meta-analysis (PRISMA) Guidelines [13]. Risk of bias of the included studies was assessed using Cochrane tool [13]. Publication bias was assessed using Funnel plot with Begg and Mazumdar test for the primary outcome only for those comparisons with at least 10 studies.

Table 1
Direct treatment comparison pooled estimates for the primary outcome

Reference interventions	Comparator interventions																						
	M	G	O	D	H	Gr	De	T	Dr	Dr/De	Dex	P	Dr/O	M/De	Dr/M	H/O	Gr/Dr	H/De	O/De	R	P/De	R/De	Gr/De	SOC
M		-	0.8 [0.4, 1.3]	-	-	-	0.2* [0.1, 0.3]	-	0.2* [0.1, 0.7]	-	-	-	-	0.2 [0.2, 1.1]	0.2* [0.04, 0.6]	-	-	-	-	-	-	-	-	1.6* [1.1, 2.4]
G			0.9 [0.3, 2.5]	-	-	-	0.6 [0.2, 1.9]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.6* [1.7, 3.9]
O				-	1.1 [2.1, 0.5]	-	0.7 [0.4, 1.1]	0.7 [0.1, 3.3]	-	-	-	0.6 [0.2, 1.7]	-	-	-	0.4* [0.2, 0.9]	-	-	0.2* [0.1, 0.4]	0.5 [0.2, 1.4]	-	-	-	4* [2.4, 6.6]
D					-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.1* [1.5, 6.4]
H						-	-	-	-	-	-	-	-	-	-	0.4* [0.2, 0.9]	-	-	-	-	-	-	-	-
Gr							0.3 [0.1, 1.1]	-	-	-	-	0.4 [0.2, 0.8]	-	-	-	-	8.7* [1, 71]	-	-	-	-	-	0.2 [0.1, 0.6]	3.7* [1.6, 8.4]
De								1.1 [0.4, 3.1]	-	-	0.7 [0.3, 1.8]	-	-	-	-	-	-	0.2* [0.1, 0.8]	0.3* [0.2, 0.5]	0* [0.1, 0.2]	-	0.39 [0.97, 0.2]	-	5.2* [3.3, 8.1]
T								-	1.7 [[0.8, 3.8]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.4* [1.6, 7.1]
Dr										-	-	-	1.1 [0.4, 2.9]	-	-	-	-	-	-	-	-	-	-	9.1* [3.7, 22.4]
Dr/De											-	-	-	-	-	-	0.1* [0, 0.6]	0.8 [0.2, 3]	-	-	-	-	0.2 [0.1, 0.7]	3.5* [1.4, 8.8]
Dex												-	-	-	-	-	-	-	-	-	-	-	-	-
P													-	-	-	-	-	-	-	0.3* [0.1, 0.9]	0.4 [0.1, 1.3]	-	-	-
Dr/O														-	-	-	-	-	-	-	-	-	-	-
M/De															-	-	-	-	-	-	-	-	-	-
Dr/M																-	-	-	-	-	-	-	-	9.2* [2.7, 31.6]
H/O																	-	-	-	-	-	-	-	-
Gr/Dr																		-	-	-	-	-	1.5 [0.2, 9.8]	28.5* [6, 135]
H/De																			-	-	-	-	-	-
O/De																				-	-	-	-	2.7 [0.9, 8]
R																					-	37* [2.1, 500]	-	-
P/De																						-	-	-
R/De																							-	-
Gr/De																								

(*continued on next page*)

Table 1 (*continued*)

Reference interventions	Comparator interventions																							
	M	G	O	D	H	Gr	De	T	Dr	Dr/De	Dex	P	Dr/O	M/De	Dr/M	H/O	Gr/Dr	H/De	O/De	R	P/De	R/De	Gr/De	SOC
																								18.5* [4.9, 70.3]

M – Metoclopramide; G – Gabapentin; O – Ondansetron; D – Dixyrazine; H – Haloperidol; Gr – Granisetron; De – Dexamethasone; T- Tropisetron; Dr – Droperidol; Dr/De – Droperidol/Dexamethasone; Dex – Dexmedetomidine; P – Palonosetron; Dr/O – Droperidol/Ondansetron; M/De – Metoclopramide/Dexamethasone; Dr/M – Droperidol/Metoclopramide; H/O – Haloperidol/Ondansetron; Gr/Dr – Granisetron/Droperidol; H/De – Haloperidol/Dexamethasone; O/De – Ondansetron/Dexamethasone; R/De – Ramosetron/Dexamethasone; R – Ramosetron; P/De – Palonosetron/Dexamethasone; R/De – Ramosetron/Dexamethasone; Gr/De – Granisetron/Dexamethasone; SOC – Standard of care; * - $P < 0.05$ (Significant).

Random-effects model was used to assess direct and mixed treatment effect estimates. Direct comparison pooled estimates were obtained by pooling studies that compared the same interventions. Indirect comparison pooled estimates were obtained by pooling studies that had atleast one comparator arm that is common to other studies. Mixed treatment comparison estimates were derived by combining both the direct and indirect pooled estimates. Odds ratio [95% confidence interval] was used as the effect estimate for all the outcome measures. Inconsistencies between direct and indirect pooled effect estimates were assessed using $\overline{H}$ statistics wherein a value of < 3 was considered as minimal, 3–6 as modest and > 6 as gross [14]. Sensitivity analyses was carried out by excluding studies with following variables in addition to the above-mentioned: studies where all the participants were only females; and there were several controversies and following which some of the articles were retracted that were authored by Fujii and so we excluded studies authored by him in one of the sensitivity analyses. Drugs were also grouped into the following drug classes for better significance: corticosteroids (dexamethasone, prednisone), serotonin-receptor antagonists (ondansetron, granisetron, tropisetron, palonosetron and ramosetron) pro-kinetic (metoclopramide) and anti-psychotics (haloperidol and droperidol). The pooled estimates were compared for the primary outcome and treatment groups were ranked based on surface area under the cumulative ranking curve (SUCRA) [15]. Trial sequential analysis was performed for the comparisons between ondansetron, and dexamethasone with placebo according to the information size achieved until date to validate the pooled estimates. O'Brien-Fleming method of alpha-spending function was used to assess the statistical significance of the pooled estimate. MetaXL was used for the analyses of pooled estimates through mixed treatment comparisons and trial sequential analysis software for analysing the adjusted pooled estimates [16,17]. Grading of evidence for key comparisons were carried out using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group approach [13].

3. Results

3.1. Search results

Four-hundred and forty two articles were retrieved of which 90 [18–48], [49-79], [80-107] were included in the systematic review and 84 in the meta-analysis. PRISMA flow diagram is depicted in Fig. 1 and the Supplementary Table 1 lists the key characteristics of the included studies. Risk of bias assessment revealed overall low risk for majority of the studies and a summary is depicted in the Supplementary Fig. 1. The included studies evaluated the following interventions: dexamethasone, metoclopramide, ondansetron, ramosetron, tropisetron, granisetron, dolasetron, palonosetron, gabapentin, haloperidol, droperidol, dixyrazine, ondansetron/dexamethasone, metoclopramide/dexamethasone, droperidol/ondansetron, granisetron/dexamethasone, dolasetron/dexamethasone, palonosetron/dexamethasone, haloperidol/ondansetron, ramosetron/dexamethasone, granisetron/droperidol, droperidol/metoclopramide and haloperidol dexamethasone.

3.2. Pooled results

3.2.1. Primary outcome

Fifty-three studies (5715 participants) were included for the analysis of complete response. Metoclopramide, gabapentin, dixyrazine, ondansetron, granisetron, dexamethasone, tropisetron, droperidol, droperidol/dexamethasone, droperidol/metoclopramide, granisetron/droperidol and granisetron/dexamethasone were observed with statistically significant pooled estimates compared to placebo in the direct comparison analysis (Table 1). In addition, haloperidol, dexmedetomidine, palonosetron, droperidol/ondansetron, metoclopramide/dexamethasone, haloperidol/ondansetron, haloperidol/dexamethasone, palonosetron/dexamethasone and ramosetron/dexamethasone were

Table 2
Mixed treatment comparison pooled estimates for the primary outcome

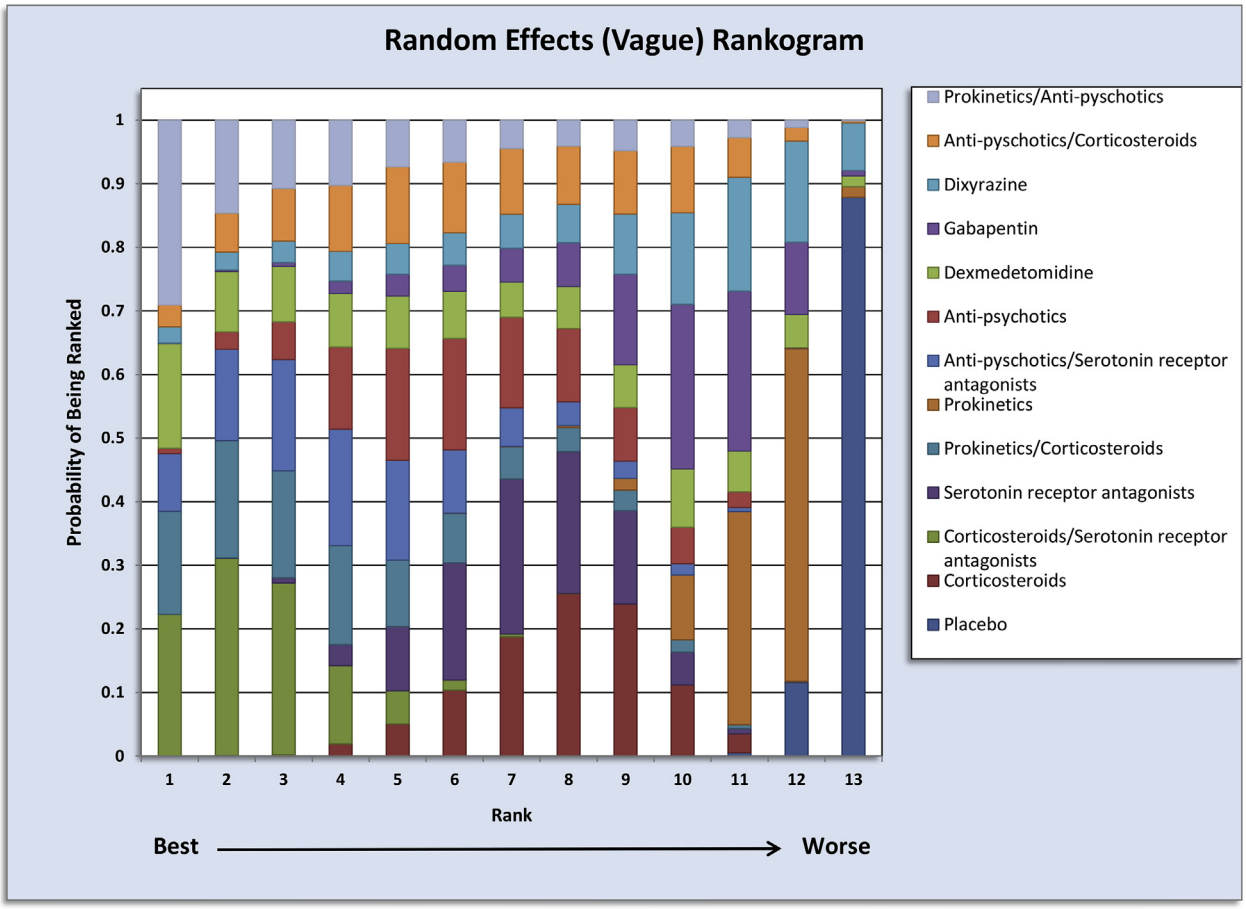
Reference interventions	Comparator interventions																						
	M	G	O	D	H	Gr	De	T	Dr	Dr/De	Dex	P	Dr/O	M/De	Dr/M	H/O	Gr/Dr	H/De	O/De	R	P/De	R/De	Gr/De	SOC
M		0.6 [0.4, 1]	0.5 [0.3, 1.1]	0.5 [0.2, 1.2]	0.8 [0.3, 2]	0.5 [0.3, 1]	0.3* [0.2, 0.5]	0.3* [0.2, 0.6]	0.2* [0.1, 0.4]	0.2 [0, 2]	0.1* [0, 0.4]	0.5 [0.2, 1.6]	0.2 [0.1, 1.1]	0.1* [0.1, 0.3]	0.2* [0.1, 0.4]	0.3* [0.1, 0.9]	0.1* [0, 0.3]	0* [0.1, 0.2]	0.1* [0, 0.6]	0.2 [0, 126]	0.2 [0.1, 1]	0.1* [0, 0.2]	0.1* [0, 0.3]	1.7* [1.1, 2.7]
G			0.7 [0.5, 1.2]	0.8 [0.4, 1.9]	0.9 [0.3, 3.1]	0.9 [0.4, 1.7]	0.5* [0.3, 0.9]	0.7 [0.4, 1.4]	0.3* [0.1, 0.8]	0.5 [0.1, 2]	0.4 [0.1, 1.9]	0.6 [0.1, 2.3]	0.3 [0.1, 1.2]	0.3 [0.1, 1.6]	0.3 [0.1, 1]	0.4 [0.1, 1.3]	0.1* [0, 0.5]	0.1* [0, 0.8]	0.3 [0.1, 1]	0.2 [0, 20.4]	0.2 [0, 1.3]	0.2 [0.1, 1]	0.1* [0, 0.6]	2.7* [1.9, 3.9]
O				1.3 [0.5, 3.1]	1 [0.6, 1.1]	1.1 [0.7, 1.9]	0.6 [0.3, 1.1]	0.9 [0.5, 1.8]	0.4* [0.2, 0.9]	0.6 [0.1, 3.4]	0.5 [0.1, 1.4]	0.6 [0.2, 1.4]	1.2 [0.2, 9.3]	0.3* [0.1, 0.7]	0.3* [0.1, 0.8]	0.4* [0.2, 0.8]	0.5 [0, 28]	0.2* [0, 0.6]	0.3* [0.1, 0.8]	0.3 [0, 2.1]	0.2 [0.1, 1.1]	0.4 [0, 63.5]	0.2* [0.1, 0.5]	2.8* [1.9, 4.3]
D					0.8 [0.3, 2.5]	2.5 [0.7, 8.5]	0.6 [0.3, 1.4]	0.9 [0.3, 2.5]	0.3 [0.1, 1.1]	0.9 [0.3, 2.9]	0.4 [0.1, 1.5]	0.5 [0.1, 1.8]	0.4 [0.1, 1.6]	0.4 [0.1, 1.5]	0.3 [0.1, 1.4]	0.3 [0.1, 1]	0.1* [0, 0.6]	0.7 [0.1, 4.2]	1.2 [0.3, 4.4]	0* [0, 0.1]	0.2 [0, 1.1]	0.2* [0.1, 0.8]	0.2* [0.1, 0.8]	3.1* [1.5, 6.4]
H						0.8 [0.3, 2.2]	0.6 [0.3, 1.5]	0.7 [0.1, 3.7]	1.1 [0.2, 7.7]	1.1 [0.3, 4]	0.4 [0.1, 1.6]	0.6 [0.2, 2.1]	1.2 [0.1, 10.2]	0.2 [0.1, 1]	0.4 [0.1, 1.9]	0.4* [0.2, 0.8]	0.1* [0, 0.8]	0.1* [0, 0.7]	0.2* [0.1, 0.6]	0.5 [0.1, 1.7]	0.2 [0, 1.3]	18.3 [0.8, 417]	0.2 [0, 1]	3.9* [1.7, 9.4]
Gr							0.6 [0.3, 1.1]	0.8 [0.3, 1.7]	0.4 [0.1, 1.4]	0.9 [0.1, 8.7]	0.2* [0, 0.9]	0.5* [0.2, 0.9]	0.4 [0.1, 2]	0.1* [0, 0.8]	0.4 [0.1, 1.8]	0.5 [0.2, 1.6]	0.4 [0, 6.7]	0.1* [0, 0.4]	0.3 [0.1, 1.3]	0.2 [0.1, 2.2]	0.1* [0, 0.6]	0.1* [0, 0.5]	0.3 [0, 2.4]	4.1* [1.4, 12]
De								1.3 [0.7, 2.4]	1 [0.5, 2.1]	0.7 [0.2, 2.2]	0.7 [0.3, 1.8]	0.8 [0.2, 3.8]	2 [0.4, 10.5]	0.7 [0.3, 1.7]	0.7 [0.3, 1.9]	0.6 [0.2, 1.6]	0.3 [0, 11.7]	0.2* [0.1, 0.6]	0.4 [0.1, 1.1]	0.3 [0, 21.3]	0.4 [0.1, 1.9]	0.4* [0.2, 1]	0.5 [0.1, 2.5]	4.9* [2.6, 9.2]
T									1.1 [0.2, 5.1]	0.6 [0.2, 2.2]	0.6 [0.1, 2.5]	0.9 [0.1, 6.2]	1.8 [0.5, 6.5]	0.4 [0.1, 2.1]	0.4 [0.1, 1.6]	0.6 [0.1, 3.7]	0.1* [0, 0.7]	0.2 [0, 1]	0.5 [0.2, 1.4]	0.2 [0, 22.1]	0.4 [0.1, 3.3]	0.3 [0.1, 1.3]	0.2 [0, 0.8]	5.1* [2.5, 10]
Dr										2.6 [0.7, 9.5]	0.5 [0.1, 2.8]	0.5 [0.1, 4.2]	1 [0.4, 2.9]	0.9 [0.2, 4.4]	0.9 [0.3, 2.8]	0.4 [0.1, 2.5]	0.3 [0.1, 1.9]	0.2 [0, 1.1]	3.4 [0.8, 14.3]	0* [0, 0.2]	0.2* [0, 2.2]	0.3 [0.1, 1.5]	0.5 [0.1, 2.5]	5.3* [2, 13]
Dr/De											2.3 [0.5, 11.2]	0.4 [0.1, 2.7]	0.4 [0.1, 2.1]	1.7 [0.3, 9.2]	0.4 [0.1, 1.8]	0.4 [0.1, 1.3]	0.1* [0, 0.4]	0.8 [0.3, 2.3]	1.1 [0.4, 2.9]	0* [0, 0.8]	0.2* [0, 1.4]	1.3 [0.3, 6.1]	0.2* [0.1, 0.5]	5.4* [2.2, 13]
Dex												1.9 [0.3, 10]	3 [0.4, 20.3]	0.7 [0.3, 3.4]	0.8 [0.3, 4.3]	0.9 [0.2, 3.6]	0.3 [0, 1.8]	0.3 [0.1, 1.7]	0.4 [0.1, 1.3]	0* [0, 0.3]	0.5 [0.1, 3.6]	0.6 [0.1, 2.2]	0.4 [0.1, 2.3]	7.6* [2.6, 22]
P													1.9 [0.2, 18.4]	0.4 [0.1, 1.8]	0.7 [0.1, 3.6]	0.7 [0.2, 2.3]	23.4* [2.4, 225.4]	0.2 [0.1, 1.2]	0.3 [0.1, 1.1]	0.4 [0.2, 1.1]	0.4 [0.1, 1.3]	11.9 [0.6, 256]	0.5 [0.1, 1.9]	7.9* [3.5, 17]
Dr/O														0.9 [0.1, 5.8]	1 [0.2, 6]	0.3 [0.1, 3.1]	0.3 [0, 2.5]	0.2 [0, 1.4]	3.4[0.6, 19.4]	0.1* [0, 0.2]	0.2 [0.1, 2.6]	0.3 [0, 2]	0.5 [0.1, 3.2]	8.9* [2.3, 34]
M/De															0.9 [0.2, 4.5]	1.7 [0.4, 7.1]	0.4 [0.1, 2.8]	0.5 [0.1, 2.7]	0.6 [0.2, 2.1]	0.1* [0, 0.5]	1 [0.1, 7]	0.8 [0.2, 3.6]	0.6 [0.1, 3.6]	9.2* [3.9, 21]
Dr/M																1 [0.2, 4.5]	0.3 [0, 2.4]	0.2 [0.1, 1.4]	3.5 [0.7, 18.2]	0.1* [0, 0.3]	0.5 [0.1, 4.2]	0.4 [0.1, 2.1]	0.5 [0.1, 3.1]	9.3* [3.8, 22]
H/O																	0.3 [0.1, 2.1]	0.4 [0.1, 1.8]	0.5 [0.2, 1.5]	1.2 [0.3, 4.4]	0.6 [0.1, 3.3]	45.3* [1.96-1040]	0.5 [0.1, 2.7]	9.7* [3.8, 24]
Gr/Dr																		6.4 [0.8, 51]	10.8* [1.6, 72.5]	0.1* [0, 0.2]	0.1* [0, 0.2]	2.1 [0.3, 13.7]	0.7 [0.1, 4.8]	10 [0.7, 159]
H/De																								

(*continued on next page*)

Table 2 (*continued*)

Reference interventions	Comparator interventions																						
	M	G	O	D	H	Gr	De	T	Dr	Dr/De	Dex	P	Dr/O	M/De	Dr/M	H/O	Gr/Dr	H/De	O/De	R	P/De	R/De	Gr/De	SOC
																			1.2 [0.3, 4.7]	0.1 [0, 1.1]	1.6 [0.2, 12.3]	1.7 [0.4, 8]	0.2 [0.1, 1.6]	11.7* [2.4, 58]
O/De																				1.3 [0, 136]	1.1 [0.2, 6]	1.4 [0.5, 4.1]	0.1* [0, 0.8]	12* [4.1, 40]
R																					1.2 [0.2, 5.9]	36.7* [4.6, 294]	26.4* [1.1, 652]	13 [0.1, 1600]
P/De																						31.8* [1.2, 856]	1.3 [0.2, 8]	16* [3.6, 86]
R/De																							0.7 [0.1, 3.1]	13* [4.9, 37]
Gr/De																								19* [8.3, 44]

M – Metoclopramide; G – Gabapentin; O – Ondansetron; D – Dixyrazine; H – Haloperidol; Gr – Granisetron; De – Dexamethasone; T- Tropisetron; Dr – Droperidol; Dr/De – Droperidol/Dexamethasone; Dex – Dexmedetomidine; P – Palonosetron; Dr/O – Droperidol/Ondansetron; M/De – Metoclopramide/Dexamethasone; Dr/M – Droperidol/Metoclopramide; H/O – Haloperidol/Ondansetron; Gr/Dr – Granisetron/Droperidol; H/De – Haloperidol/Dexamethasone; O/De – Ondansetron/Dexamethasone; R/De – Ramosetron/Dexamethasone; R – Ramosetron; P/De – Palonosetron/Dexamethasone; R/De – Ramosetron/Dexamethasone; Gr/De – Granisetron/Dexamethasone; SOC – Standard of care; * - $P < 0.05$ (Significant).



Treatment	SUCRA
Corticosteroids/Serotonin receptor a	0.8716
Prokinetics/Corticosteroids	0.7611
Prokinetics/Anti-pyschotics	0.7494
Anti-pyschotics/Serotonin receptor a	0.7297
Dexmedetomidine	0.6009
Anti-psychotics	0.5646
Anti-pyschotics/Corticosteroids	0.5435
Serotonin receptor antagonists	0.4847
Corticosteroids	0.4234
Dixyrazine	0.3398
Gabapentin	0.2879
Prokinetics	0.133
Placebo	0.01058

Fig. 2. Rankogram plot. Corticosteroids/serotonin receptor antagonists had the highest probability of being 'best' in this pool of interventions.

observed with better complete response rate in the mixed treatment comparison analysis (Table 2). Analysis was also carried out grouping the interventions into individual drug classes as described above (Supplementary Table 2). It can be observed that corticosteroids/serotonin receptor antagonists had the highest point estimate against placebo as well as being associated with significantly better rate of complete response against many other drugs. Also, SUCRA plot revealed corticosteroids/serotonin receptor antagonists had the highest probability of being the 'best' in this pool of interventions (Fig. 2).

3.2.2. *Secondary outcomes*

A summary of mixed treatment pooled estimates for the secondary outcomes is provided in Table 3. Various drugs were observed with significant pooled estimates compared to placebo in all the outcomes except adverse events.

Table 3
Mixed treatment comparison pooled estimates for the secondary outcomes compared to placebo.

Interventions	Secondary outcomes [Total number of studies; Total number of participants]					
	Incidence of nausea at 6 h [12; 1409]	Incidence of vomiting at 6 h [13; 1314]	Incidence of nausea at 24 h [42; 4355]	Incidence of vomiting at 24 h [46; 4711]	Use of rescue anti-emetics [44; 5243]	Adverse events [11; 1273]
Granisetron/Droperidol	0.02* [0, 0.5]	0.26 [0, 19.5]	–	–	0.02* [0, 0.13]	–
Haloperidol/Dexamethasone	0.04* [0, 0.4]	0.01* [0, 0.13]	0.06* [0.02, 0.23]	0.05* [0.01, 0.2]	–	–
Ondansetron/Dexamethasone	0.13* [0.06, 0.3]	0.06* [0.02, 0.2]	0.12* [0.06, 0.24]	0.06* [0.02, 0.21]	0.05* [0.02, 0.11]	0.51 [0.24, 1.1]
Granisetron	0.19* [0.06, 0.67]	0.27* [0.08, 0.97]	0.34* [0.15, 0.76]	0.21* [0.11, 0.43]	0.2* [0.1, 0.36]	1.1 [0.5, 2.5]
Droperidol	0.2* [0.06, 0.73]	0.28* [0.08, 0.92]	0.86 [0.34, 2.22]	0.66 [0.36, 1.21]	0.5* [0.26, 0.95]	–
Droperidol/Metoclopramide	0.2* [0.06, 0.73]	0.18* [0.04, 0.81]	–	–	0.16* [0.08, 0.33]	–
Ondansetron	0.28* [0.14, 0.57]	0.34* [0.15, 0.76]	0.36* [0.25, 0.52]	0.2* [0.12, 0.33]	0.32* [0.25, 0.42]	0.6 [0.31, 1.1]
Droperidol/Dexamethasone	0.33 [0.08, 1.37]	0.08* [0.01, 0.47]	0.1* [0.03, 0.34]	0.07* [0.02, 0.24]	0.08* [0.02, 0.35]	–
Dexamethasone	0.42* [0.23, 0.78]	0.17* [0.06, 0.43]	0.29* [0.22, 0.38]	0.23* [0.09, 0.61]	0.28* [0.22, 0.36]	0.7 [0.3, 1.72]
Prednisone	0.61 [0.34, 1.1]	0.37* [0.18, 0.76]	0.89 [0.51, 1.57]	0.5* [0.25, 0.94]	–	–
Metoclopramide	1 [0.44, 2.2]	0.56 [0.24, 1.27]	0.54 [0.28, 1.01]	0.45* [0.21, 0.96]	0.53* [0.31, 0.9]	0.07 [0, 1.63]
Palonosetron/Dexamethasone	–	–	0.06* [0.02, 0.2]	0.05* [0.01, 0.42]	0.09* [0.02, 0.39]	0.1 [0.01, 1.3]
Granisetron/Dexamethasone	–	–	0.08* [0.01, 0.91]	0.1 [0.01, 1.27]	0.02* [0.01, 0.11]	1 [0.2, 5]
Dexmedetomidine	–	–	0.2* [0.06, 0.7]	0.15 [0.02, 1]	–	–
Palonosetron	–	–	0.21* [0.08, 0.54]	0.13* [0.04, 0.45]	0.42 [0.16, 1.11]	0.15 [0.02, 1]
Haloperidol/Ondansetron	–	–	0.24* [0.08, 0.75]	0.09* [0.02, 0.45]	0.15* [0.05, 0.44]	–
Dixyrazine	–	–	0.25* [0.11, 0.58]	0.65 [0.22, 1.91]	–	–
Ramosetron	–	–	0.25* [0.09, 0.69]	0.23* [0.06, 0.94]	0.21* [0.1, 0.47]	–
Dimenhydrinate	–	–	0.3* [0.11, 0.81]	0.5 [0.08, 3.17]	0.41 [0.16, 1.11]	–
Metoclopramide/ Dexamethasone	–	–	0.3 [0.08, 1.1]	0.24 [0.06, 1.05]	0.19 [0.03, 1.1]	–
Tropisetron	–	–	0.33* [0.16, 0.65]	0.12* [0.04, 0.38]	0.23* [0.1, 0.52]	0.54 [0.03, 10.33]
Haloperidol	–	–	0.34 [0.12, 1.01]	0.28 [0.06, 1.26]	0.5 [0.11, 2.22]	–
Droperidol/Ondansetron	–	–	1.26 [0.34, 4.67]	0.03* [0.01, 0.13]	0.11* [0.04, 0.26]	–
Hysocine TD patch	–	–	1.52 [0.54, 4.26]	0.97 [0.3, 3.28]	0.66 [0.11, 4.1]	–
Perphenazine	–	–	–	–	0.12 [0.01, 1.1]	–
Gabapentin	–	–	–	–	0.38* [0.27, 0.55]	–

All the estimates are mentioned in odds ratio [95% confidence intervals]; * - P < 0.05 (statistically significant).

3.3. Sensitivity analyses

Twenty-seven studies (2734 participants) mentioned prior anti-emetic use as an exclusion criteria and analysis of data from these studies did not reveal any significant difference from the overall results (Supplementary Fig. 2). Four studies reported administering anti-emetics at the end of surgery and exclusion of data from these studies did not significantly influence the pooled estimates compared to overall analysis (Supplementary Fig. 3). Twenty studies reported administering propofol as a general anaesthetic agent for LC and exclusion of data from these studies did not deviate the pooled estimates significantly compared to overall analysis (Supplementary Fig. 4). Similarly, four studies were carried out exclusively in females and removal of these data did not significantly alter the pooled estimates (Supplementary Fig. 5). Three studies were carried out by Fujii and exclusion of these studies also did not alter the pooled estimates significantly (Supplementary Fig. 6).

3.4. Publication bias

Adequate numbers of studies were available only for dexamethasone and ondansetron compared to placebo for the primary outcome. No bias was detected both by Funnel plot and Begg and Mazumdar tests for both dexamethasone (P = 0.1) and ondansetron (P = 0.06) (Supplementary Figs. 7 and 8 respectively).

3.5. Trial sequential analysis

There were adequate studies only for the comparison of ondansetron and dexamethasone with placebo for the primary outcome to conduct trial sequential analysis and the current evidence is adequate to confirm the significant benefit for both these drugs (Supplementary Figs. 9 and 10).

3.6. Grading the evidence

Grading the strength of pooled estimated for key comparisons for complete response was carried out (Table 4). Moderate quality was observed for dexamethasone and ondansetron while either very low or not assessable for other drugs.

4. Discussion

The present study was undertaken to generate evidence-based estimates for anti-emetics in LC from 90 randomized clinical trials. Various drugs were observed with significantly better complete response rate compared to placebo as is with secondary outcomes. Corticosteroid/serotonin receptor antagonists were observed with the highest probability of being the 'best' in this pool. Sensitivity analyses provided similar results when compared to the overall results. The evidence is adequate to confirm the benefits of dexamethasone and ondansetron only.

A recent consensus from the Society of Ambulatory Anaesthesia recommends prophylactic anti-emetic for patients undergoing abdominal surgeries with any of the following risk factors: female gender, history of PONV, opioid use [108]. Several anti-emetics are recommended by the Society as prophylaxis for patients undergoing major abdominal surgeries under general anaesthesia and they are supported by the existing meta-analyses. Nevertheless, the drawbacks of the current evidence are: not all the prophylactic anti-emetic regimens were compared in a single platform; publication bias was not assessed; grading the evidence for key comparisons were not carried out; and adequacy of the evidence by trial sequential analysis validating the pooled estimates was not assessed. The present network meta-analysis is the first in this field with due considerations taken to address the above-mentioned methodological flaws. Despite observing the benefits for several anti-emetics, the present evidence in the literature is

Table 4
Grading the evidence for key comparisons for the primary outcome.

Comparisons	Illustrative comparative risks (95% confidence intervals)		Effect estimate and quality of evidence for direct comparisons	Effect estimate and quality of evidence for mixed treatment comparisons
	Assumed risk[b]	Corresponding risk[a]		
Metoclopramide	333 per 1000	444 per 1000 (333–545)	1.6 [1.1, 2.4] ⊕⊖⊖⊖; Very low [c, d, e]	1.7 [1.1, 2.7] ⊕⊖⊖⊖; Very low [c, d, e]
Gabapentin		564 per 1000 (459–661)	2.6 [1.7, 3.9] ⊕⊖⊖⊖; Very low [c, d, e]	2.7 [1.9, 3.9] ⊕⊖⊖⊖; Very low [c, d, e]
Ondansetron		666 per 1000 (545–767)	4 [2.4, 6.6] ⊕⊕⊕⊖; Moderate[e]	2.8 [1.9, 4.3] ⊕⊕⊕⊖; Moderate[e]
Dixyrazine		607 per 1000 (430–762)	3.1 [1.5, 6.4] Not assessed	3.1 [1.5, 6.4] Not assessed
Granisetron		649 per 1000 (444–807)	3.7 [1.6, 8.4] ⊕⊖⊖⊖; Very low [c, d, e]	4.1 [1.4, 12] ⊕⊖⊖⊖; Very low [c, d, e]
Dexamethasone		722 per 1000 (622–802)	5.2 [3.3, 8.1] ⊕⊕⊕⊖; Moderate[e]	4.9 [2.6, 9.2] ⊕⊕⊕⊖; Moderate[e]
Tropisetron		629 per 1000 (444–780)	3.4 [1.6, 7.1] ⊕⊖⊖⊖; Very low [c, d, e]	5.1 [2.5, 10] ⊕⊖⊖⊖; Very low [c, d, e]
Droperidol		820 per 1000 (649–918)	9.1 [3.7, 22.4]; Not assessed	5.3 [2, 13] Not assessed
Droperidol/Dexamethasone		636 per 1000 (411–815)	3.5 [1.4, 8.8] Not assessed	5.4 [2.2, 13] Not assessed
Droperidol/Metoclopramide		821 per 1000 (574–940)	9.2 [2.7, 31.6] Not assessed	9.3 [3.8, 22] Not assessed
Granisetron/Droperidol		934 per 1000 (750–946)	28.5 [6, 35] Not assessed	10 [0.7, 159] Not assessed
Granisetron/Dexamethasone		902 per 1000 (710–973)	18.5 [4.9, 70.3] Not assessed	19 [8.3, 44] Not assessed
Haloperidol		661 per 1000 (459–824)	–	3.9 [1.7, 9.4] Not assessed
Dexmedetomidine		791 per 1000 (565–917)	–	7.6 [2.6, 22] Not assessed
Palonosetron		798 per 1000 (636–895)	–	7.9 [3.5, 17] Not assessed
Droperidol/Ondansetron		816 per 1000 (535–944)	–	8.9 [2.3, 34] Not assessed
Metoclopramide/Dexamethasone		821 per 1000 (661–913)	–	9.2 [3.9, 21] Not assessed
Haloperidol/Ondansetron		830 per 1000 (655–923)	–	9.7 [3.8, 24] Not assessed
Haloperidol/Dexamethasone		854 per 1000 (545–967)	–	11.7 [2.4, 58] Not assessed
Ondansetron/Dexamethasone		857 per 1000 (591–952)	–	12 [4.1, 40] Not assessed
Palonosetron/Dexamethasone		889 per 1000 (643–977)	–	16 [3.6, 86] Not assessed
Ramosetron/Dexamethasone		866 per 1000 (710–949)	–	13 [4.9, 37] Not assessed

Not assessed – Due to very serious limitations in the total number of studies/imprecision of the estimates/not being a first-order loop in case of mixed treatment comparison estimates, grading of the strength of estimates was not attempted.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Very low quality: We are very uncertain about the estimate.

[a] Corresponding risks are based on the effect estimates from direct comparisons where available and from mixed treatment comparison estimates, in case direct comparison pooled estimates were not available.

[b] Assumed risk was the median control group risk across the studies.

[c] Downgraded one level for small sample size.

[d] Downgraded one level as publication bias could not be assessed.

[e] Downgraded one level as some of the studies were associated with high risk of bias.

adequate to confirm the efficacy of dexamethasone and ondansetron only. Combination of anti-emetics is preferred in high-risk patients as more than one receptor-type is involved in mediating PONV [109]. Commonly used combination of anti-emetics include drugs from serotonin receptor antagonists, corticosteroids, phenothiazines and prokinetics [110]. Of these, corticosteroids/serotonin receptor antagonists were observed to be the best in the pool. However, this combination shall be limited to patients with high-risk category and not used as first-line therapy. Further, no increased risk of adverse events was observed with this combination compared to placebo while the same could not be assessed for others. In propofol-induced general anaesthesia, such combined anti-emetics were shown to be more beneficial in reducing PONV [111].

Willingness to pay to avoid PONV was observed to be 100 USD in US, 80 in UK [112,113]. On the other hand, a more recent study from Netherlands has estimated WTP to be 17 USD and there is no data from other nations [114]. However, there are no studies evaluating the cost-efficacy of prophylactic anti-emetics particularly in LC. Considering the availability of generic drugs in almost all the commonly used anti-emetics for PONV, depending on the availability of resources, each hospital can adopt listing the anti-emetics that has shown significant benefits in the present meta-analysis. However, more cost-effective studies comparing the different anti-emetic regimens are needed.

The present meta-analysis included the maximum number of studies

and so the patients until date in this field. The importance of the results of present meta-analysis has to be interpreted in the clinical context that it might take several years to generate the relative effect estimates through head-to-head clinical trials comparing all the potential anti-emetics for PONV in LC. However, the study has the following limitations: EMBASE could not be searched for potential studies due to access constraints; and studies that evaluated different general anaesthetics for reducing PONV were not included.

To conclude, the relative effect sizes of prophylactic anti-emetics for PONV in patients undergoing LC were estimated. Moderate quality of evidence was observed for dexamethasone and ondansetron. However, choice of single anti-emetic for low-to-moderate risk categories should depend on the availability and the cost, while in the combination, corticosteroids/serotonin receptor antagonists is preferable especially for high-risk category.

Ethical approval

Ethics approval was not needed as it is a network meta-analysis.

Sources of funding

No funding was obtained.

Author contribution

Substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data – KS, GS; drafting the article or revising it critically for important intellectual content – KS, GS; final approval of the version to be published – KS, GS; and agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved – KS, GS.

Conflicts of interest

None.

Trial registry number

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Guarantor

Kannan SRidharan.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

The current work is a network meta-analysis and so it involves pooling of data from the included studies. Hence, for the original data, the cited studies as in the table of included studies in the electronic supplementary file can be accessed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.07.002.

Ninety articles were included in the systematic review and 84 in the final meta-analysis.

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