SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Efficacy of dexmedetomidine in postoperative nausea and vomiting in laparoscopic bariatric surgery: A systematic review and meta-analysis of randomised clinical trials

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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) is a common side effect of all types of surgeries, especially so in bariatric surgery. Dexmedetomidine (DX) is an α2-agonist that may be useful as an adjunct prophylactic medication for PONV. This meta-analysis aims to evaluate the efficacy of DX in reducing the incidence and severity of PONV in laparoscopic bariatric surgeries.

Materials and Methods: Databases were searched for articles with the determined MESH terms and keywords before February 2022. Identified articles were screened and 13 randomised clinical trials (RCTs) were included in this meta-analysis based on the inclusion criteria. Data were extracted from the articles and statistical analysis was performed using Review Manager.

Results: Administration of DX significantly reduced the incidence of PONV and Numerical Rating Scale (NRS) scores for PONV. The outcome was probably due to the intrinsic sympatholytic effect of the medication, reduction of postoperative pain and total postoperative opioid usage. DX showed better efficacy as PONV prophylaxis if the duration of surgery was < 120 minutes. Delivery of DX as a continuous infusion without a loading dose before infusion was found to be effective in reducing PONV compared to infusion after a loading dose.

Conclusion: Administration of DX can reduce the incidence of PONV in patients undergoing laparoscopic bariatric surgery. However, further studies are required to investigate the optimal dose of DX as an antiemetic, considering its side effects to increase the applicability of our results in future guidelines for laparoscopic bariatric surgery.

KEYWORDS:
PONV, Laparoscopic bariatric surgery, Dexmedetomidine, Meta-analyses

INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common side effect of anaesthesia in all types of surgeries and is often rated as worse than pain related to surgery itself.[1] It is one of the most common causes of patient dissatisfaction after anaesthesia, with reported incidences of 30% in all post-surgical patients and up to 80% in high-risk patients.[2] Various risk factors for PONV have been identified, including the female gender, history of PONV, motion sickness, duration of anaesthesia with volatile anaesthetics, postoperative opioids and laparoscopic surgeries.[3]

Obesity in the global population is growing at an alarming rate and Malaysia is not an exception. According to the latest National Health and Morbidity Survey 2019, obesity in the Malaysian population was 19.7%.[4] A high prevalence of obesity increases the need for bariatric surgery, as it is the most effective treatment for morbid obesity with a BMI of >35 kg/m^2, resulting in sustained weight loss and reduced obesity-related comorbidities.[5]

However, there are no currently established clear guidelines that can effectively reduce PONV in patients going for bariatric surgery. Conventional guidelines currently recommend the use of multimodal prophylaxis in patients with risk factors, one such being a combination of ondansetron and dexamethasone.[6] Even with the current supra-optimal prophylaxis, Halliday et. al found that PONV could go up to 59% in bariatric surgery patients.[7] This could partly be due to inadequate prophylaxis or inadequate published evidence to guide clinicians on the choice of the optimal combination for individual patients.

The efficacy of new drugs should be explored in view of the ineffective prophylaxis in the current state. Dexmedetomidine (DX) is an α2-adrenoreceptor agonist with sedative, analgesic, and sympatholytic properties. It has been used for bariatric as well as non- bariatric surgeries to suppress PONV, and as a sedative in critically ill patients ventilated in intensive care. Currently, multiple promising trials show the efficacy of DX in preventing PONV. To our knowledge, there is no conclusive review to ascertain the effectiveness of the results. Hence, this meta-analysis aims to evaluate the current studies on the role of DX compared with other antiemetics prophylaxis for reducing the incidence of PONV in individuals undergoing laparoscopic bariatric surgery.

MATERIALS AND METHODS

This meta-analysis of randomised clinical trials (RCTs) was performed following the Preferred Reporting Items for

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Systematic Reviews and Meta-Analyses (PRISMA) statement and the review protocol can be found in the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42022309684.

Search Strategy and Study Selection

A systematic search was conducted using the following online databases: PubMed, SpringerLink, EBSCOhost, Scopus, Science Direct and Ovid MEDLINE to identify relevant studies available from inception to February 2022. We searched for randomised controlled trials on the use of DX for PONV prophylaxis for laparoscopic bariatric surgeries.

The search strategy consisted of Medical Subject Headings (MeSH) terms ("dexmedetomidine AND laparoscopic bariatric surgery AND postoperative nausea and vomiting", "dexmedetomidine AND postoperative nausea and vomiting") and free text words ("dexmedetomidine AND laparoscopic bariatric surgery AND postoperative nausea and vomiting", "dexmedetomidine AND laparoscopic bariatric surgery AND postop nausea and vomiting", "dexmedetomidine AND laparoscopic bariatric surgery"). A search for grey literature was conducted in the OpenGrey database and manual search was also performed in the reference lists of the relevant studies. A reference list of searched data was created, and the abstracts were reviewed by two independent authors (THY, TJH). Controversy over the eligibility of an abstract was resolved by another author (THS).

Inclusion and Exclusion Criteria

All RCTs comparing the safety and efficacy of DX to any other drugs (placebo, opioids, dexamethasone, clonidine, xylocaine) in laparoscopic bariatric surgery under general anaesthesia were included. All studies that reported PONV or made a distinction between nausea or vomiting (considered as PONV) were included. Duplicated articles, editorial articles, case reports, reviews, comments, guidelines, wrong population, wrong drug, wrong study type, non-English, non-laparoscopic bariatric surgery and conference abstracts were excluded from this review.

Data Extraction and Quality Assessment

Available data from chosen RCTs were maximally extracted and tabulated on Excel sheets by several authors (THY, TJH). The data extracted were authors, country, publication year and participant's characteristics, study design, type of surgery, gender, body mass index (BMI), ASA physical status classification, treatment regimen, duration of surgery, duration of anaesthesia, incidence of postoperative nausea and vomiting, numerical nausea score, time to discharge from PACU, total postoperative opioid dose, total volatile agent usage, pain score, total intraoperative opioid usage and postoperative analgesia. The authors were contacted via electronic mail in an attempt to retrieve the missing information.

Critical appraisal of all selected studies was done using the Cochrane Risk of Bias Tool as shown in Figure 1 and 2.

Data Analysis

All statistical analyses were performed using the Review Manager (RevMan version 5.4.1, The Cochrane Collaboration, 2020) software. The primary goal of this meta-analysis was to compare the incidence of PONV after the use of DX and other anti-emetics. The NRS used to measure the severity of PONV in the identified studies was used for data analysis. Secondary outcomes were duration of anaesthesia, duration of surgery, time to safe extubation, time to discharge from post-anaesthesia care unit (PACU), total intraoperative opioid use and total postoperative analgesia. Subgroup analyses of intraoperative comparator i.e., DX versus placebo were done to improve the homogeneity between the groups. Data were only pooled if an outcome was identified in at least three RCTs. Relative risk or risk ratio (RR) with a 95% confidence level was measured for dichotomous outcomes while mean difference (MD) or standard mean difference (SMD) with standard deviation (SD) was measured for continuous outcomes.

A funnel plot was created to detect publication bias. Statistical heterogeneity was assessed using the χ^2 test and the I^2 statistic. A two-tailed p-value of < 0.05 was accepted as statistically significant. An I^2 of less than 25% is viewed as low heterogeneity, between 25% and 50% as moderate, and over 50% as high heterogeneity. Random-effect model was used if significant heterogeneity was detected with the assumption that a single true effect size did not occur across the included studies. Otherwise, a fixed-effect model was used. Data analysis was carried out by two investigators (NHT, THY). Resolution of any discrepancies was conducted by discussion with the third investigator (THS).

This research was presented, and approval was obtained from the International Medical University Joint-Committee on Research and Ethics. (IMUJC); Project ID No.: IMU 551-2022.

RESULTS

Study Selection

A total of 295 relevant publications were identified through a systematic literature search and five were manually extracted from relevant literature review articles.[8-12] From these 13 RCTs were selected for review.The characteristics of each study were extracted and documented (Tables I and II) and a summary of the outcomes extracted are shown in Table III. The risk of bias for each trial was assessed as shown in Figures 1 and 2. The risk of bias in most domains was graded as low. However, all trials were graded as 'unclear risk' under the 'Other bias' domain. Overall, the quality of the included trials was graded as moderate because of the high risk of selective reporting bias in some and the unclear risk of other bias in all studies. A summary of the outcomes of the analysis is shown in Figures 1 and 2. The detail of data extraction is added as a supplementary file and in Tables I and II.

The incidence of PONV post-laparoscopic bariatric surgery comparing DX with other antiemetics was reported in 12 articles. Overall, there was a significant risk reduction in the incidence of PONV with the use of DX (RR = 0.48 [0.41, 0.57]; $p < 0.00001$] as shown in Figure 4. All compared medications

showed risk reduction except clonidine which suggested no difference in risk of incidence of PONV. The lowest risk of PONV was observed when compared to dexamethasone (RR = 0.26 [0.11 – 0.63]; p = 0.003, followed by desflurane (RR = 0.28 [0.14. 0.54]; p = 0.0002, opioid (RR = 0.47 [0.36,0.62]; p < 0.00001), and lastly placebo (RR = 0.48 [0.37, 0.62]; p < 0.00001).

An average of 120 minutes were taken as the expected duration of laparoscopic bariatric surgery averaged from the duration of surgery documented in the included studies (Figure 5). There was a significant reduction in the incidence of PONV with the use of DX if the duration of surgery was < 120 minutes (RR = 0.38 [0.26, 0.57]; p < 0.00001). On the other hand, there was no difference in the incidence of PONV if the surgery was > 120 minutes (RR = 0.62 [0.28, 1.34]; p = 0.22).

Some selected trials prescribed an IV bolus DX before starting an infusion (Figure 6).[10,11,13,16,19] There was a significant risk reduction in the incidence of PONV in both groups. However, risk reduction without IV bolus DX before an infusion (RR = 0.42 [0.25, 0.71]; p = 0.001) was more compared to those with IV bolus followed by infusion (RR = 0.51 [0.40, 0.65]; p = < 0.0001).

RCTs were further analysed by subgrouping the articles based on the percentage of male gender in the study participants. This was because most of the studies did not state the exact number of males and females who participated in the trials. Attempts were made to contact the respective authors with no response. As illustrated in Figure 7, the risk of PONV was reduced in both male-predominant (RR = 0.42 [0.30, 0.59]; p < 0.00001) and female-predominant (RR = 0.45 [0.35, 0.58]; p < 0.00001) groups with the use of DX.

The heterogeneity across the 11 studies was low to moderate.

Numerical Rating Scale of PONV

Five RCTs measured the severity of PONV using NRS. Similar subgroup analyses on PONV were performed. However, one of the studies interpreted the data using the median and interquartile range, hence the result from that study was excluded in the sub-group analyses.[21]

Analysis showed a significant difference in the standard mean difference (SMD) of NRS for PONV (SMD = -1.21 [-1.89, - 0.54]; p = 0.0004). SMD was also found to be significantly lower when DX was compared to dexamethasone (SMD = -2.33 [-2.94, -1.73]; p = 0.0001). There was high total heterogeneity (I^2 = 84%) and subgroup heterogeneity (I^2 = 94.3%) (Figure 8).

Considering the duration of surgery, the SMD of NRS for PONV was significantly reduced in the > 120-minute subgroup (SMD = -1.53 [-3.0, 0.04]; p = 0.06). No difference in NRS subgroup analysis was found with a duration of surgery < 120 minutes (SMD = -1.52 [-3.09, -0.04]; p = 0.06. High total heterogeneity (I^2 = 89%) was detected but subgroup heterogeneity was not significant (Figure 9).

Groups with a higher number of female participants scored lower on the NRS for PONV with the use of DX (SMD = -0.97 [-1.32, -0.62], p < 0.00001) compared to the groups in which there were a higher number of males (SMD = -01.53 [-3.09, 0.04], p = 0.06). It appears that females responded better to the DX than the males. A low subgroup difference was detected although there was a high total heterogeneity (I^2 = 84%) (Figure 10).

Total Dose of Postoperative Analgesia Used

Six studies documented the total dose of analgesia used by the participants postoperatively. In general, DX was shown to reduce the total postoperative analgesia requirement (SMD = -1.87 [-3.31, -0.42], p = 0.01). However, subgroup analyses revealed that the total postoperative analgesia used was significantly lowered when comparing DX to placebo (SMD = -4.04 [-6.99, -1.09]). No difference in SMD was noted when DX was compared to dexamethasone and opioids. High total and subgroup heterogeneity were detected (Figure 11).

There was no difference in the SMD of total postoperative analgesia used even when participants were given an IV bolus DX before DX infusion. The subgroup heterogeneity was low despite a high total difference (Figure 12).

Time to Discharge from Post-Anaesthesia Care Unit (PACU)

Time to discharge from PACU was recorded in seven studies, one study was not included for pooled analysis as the result was reported in the median and interquartile range. DX significantly reduced the time to discharge from the PACU (SMD = -0.36 [CI -0.57, -0.15], p = 0.001) (Figure 13). Subgroup analysis of DX versus placebo and opioid respectively, DX only showed a significant reduction in the time to discharge from PACU when compared to placebo (SMD = -0.83 [CI-1.17, -0.48], p < 0.00001). There were high subgroup differences and moderate total heterogeneity. No significant difference in the time to discharge from PACU was seen when DX was compared to opioids.

The use of IV bolus and no bolus before initiating infusion of DX during induction did not influence the time to discharge from PACU. Moderate total heterogeneity and low subgroup heterogeneity were noted (Figure 14).

Total Intraoperative Opioid Used

Seven studies reported data on the total dose of intraoperative opioids used. Pooled analysis showed that the use of DX intra-operatively did not affect the amount of intraoperative opioid consumption (SMD = -1.14 [-2.47, 0.19]; p = 0.09). Subgroup analysis showed that only when compared to dexamethasone, DX had a significant reduction in total intraoperative opioid use (SMD = -1.83 [-2.39, -1.28], p < 0.00001). High total and subgroup heterogeneity were detected (Figure 15).

When the outcome of IV bolus DX followed by infusion was compared with infusion of DX without bolus the subgroup analysis revealed a significant reduction in the total amount of opioid consumption in the group without IV bolus DX (SMD = -1.70 [-3.02, -0.38], p =0.01). In contrast, no significant difference was seen in those treated with pre-infusion IV bolus DX (SMD = -0.70 [-3.04, 1.64], p = 0.56).

Table I: Characteristics of selected RCTs comparing dexmedetomidine and other antiemetics in laparoscopic bariatric surgery[8-20]

Study author and year	Country	Study design	Type of surgery	No of participants		ASA		BMI		Treatment regimens		Age		Male%		Duration of surgery (mins)		Duration of anaesthesia (mins)	
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Tufanogullari et al.	Dallas, Texas	db rct	Laparoscopic bariatric	20	20	II 14(70) III 6(30)	II 14(70) III 6 (30)	W 127± 20 H 169 ± 10	127± 25 165± 12	0.2 mcg/kg/h	NS	47±10	43±16	15%	15%	110 ± 62	116 ± 52	145 ± 63	153 ± 54
				20		II 2 (10) III 18 (90)		138± 41 169± 8		0.4 mcg/kg/h		48 ± 9		20%		107 ± 35		143 ± 51	
				20		II 4 (20) III 16 (80)		151± 36 172± 13		0.8 mcg/kg/h		40±10		45%		111±56		145±55	
Halaweh et al.	New York	db rct	Laparaoscopic bariatric	30	30	I 24(80) II 6(20)	I 28(93.3) II 2(6.7)	43.4 ± 4.4	42.5 ± 4.7	IVI 0.3 mcg/kg/h dex	IVI 3 mg/h morphine	35.2 ± 10.2	31.8 ± 8.5	23%	23%	N/A		N/A	
Ibrahim et al.	Saudi Arabia	sb rct	Laparoscopic bariatric	52	51	II 29 (56.8) III 22 (43.1)	II 35(67.3) III 17(32.9)	45.0 [43.0–46.0]	44.0 [42.0–45.0]	IV dex 0.1 ug/kg + IVI 0.5ug/kg/h + IV ketamine 0.5mg/kg	IV fentanyl1ug/kg	30 [22-36]	32 [23-39]	40.38%	37.25%	40.5 ± 9.04	43.0 ± 9.86	63.7 ± 8.61	64.8 ± 9.19
Sherif & Elsersy	Egypt	db rct	Laparoscopic bariatric	49	49	NA		44 ± 3 (43.2-45)	45±4 (42.9-45.1)	IV dex 1ug/kg + IVI 0.4ug/kg/h	NS	39±9	39±8	16.33%	22.45%	N/A		N/A	
				46				44±4 (43.3-46)		IV xylocaine 2 mg/kg + 1.5 mg/kg/h		38±9		28.26%					
Bakhamees et al.	Middle East	db rct	Laparoscopic bariatric	40	40	II 26	II 24	43± 6	42± 5	0.8 mcg/kg bolus, 0.4 mcg/kg/h	normal saline of same volume	30±6	29±8	53.33%	60%	157±29	155±27	N/A	
						III 14	III 16												
Sabra et al.	Saudi Arabia	db rct	Laparoscopic bariatric	36	36	I 13	I 11	W 137.9 ±8.4	W 143.2 ± 8.5	1 mcg/kg dex, odansetron 4mg, dexamethasone 8 mg	odansetron 4mg, dexamethasone 8mg	32.2± 8.3	24.1±6.7	47.22%	41.66%	121.58±33.7	138.2±22.23	174.47±36.2	153.92±33.3
						II 19	II 21	H 1.76± 0.33	H 1.7 ± 0.05										
Ziemann et al .	United states of America	sb rct	Laparoscopic bariatric	60	59	N/A		44.15 ± 7.46	45.32 ± 6.97	IV Dex 0.5 mcg/kg IVI Dex 0.1-0.3 mcg/kg/h	0.5-1 mcg fentanyl and inhalation anaesthetics	50.5± 13.7	50.4±12.4	35%	27.12%	131±69	118±50	195±73	175±57
										IVI Propofol 75-150 mcg/kg/min IV Ketamine 0.5 mg/kg									
Elbakry et al.	Egypt	DB rct	Laparoscopic sleeve gastrectomy	50	50	N/A	N/A	42.55+/-4.36	41.60+/-4.38	IVI Propofol 100-200mcg/kg/hr and Dex 0.5-1mcg/kg/hr	Inhalation desflurane and oxygen mixture	34.35+/-11.15	35.31+/-10.43	34%	30%				
Mostafa et al.	Egypt	db rct	laparoscopic bariatric	30	30	N/A	N/A	41.37 ± 6.96	39.93 ± 5.83	IV Dex 1mcg/kg IVI Dex 0.5mcg/kg.h	Normal saline	30.77±6.9	29.9±6.78	36.67%	43.33%	91.33±57.64	85.07±12.4	108.67±14.1	101.9±15.69
Naja et al.	Lebanon	db rct	Laparoscopic bariatric	30	30					IVI Dex0.5-0.8ug/kg/h	IVI Clonidine 0.8-1.2ug/kg/30min	31.21±6.9	32.13 +-9.6	43.33%	23.33%	126.03±24.6	138.01±38.1	171.5±27.6	182.3 ± 39.9
Narejo et al.	Saudi Arabia	db rct	Laparoscopic bariatric	20	20	II 16	II 16	45.05 ± 6.21	45.33 ± 6.06	IVI Dex 0.2-0.7 mcg/kg/h	IV Remifentanil 5mg	38.05± 11.33	31.45± 10.23	30%	35%	74.6±23.19	63.25±16.18	3.9±1.8 (awaken)	3.65±2.16

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				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
-						III 4	III 4												
-	Egypt	db rct	Laparoscopic bariatric			II 19	II 21	H 1.76± 0.33	H 1.7 ± 0.05	IV Dexamethasone 8mg	IV Dexamethasone 8 mg								
Salama & Abdallah				30	30	II 30	II 30	49.33+/-8.84	48.77+/-3.41	IVI Dex 0.4mcg/kg/h PO 75mg Pregabalin	Placebo capsule + normal saline infusion	33.80 ± 8.84	33.93±9.14	43.33%	36.67%	117.77±5.98	117.87±6.54	N/A	
-				46				44±4 (43.3-46)		IV Xylocaine 2 mg/kg IVI Xylocaine 1.5 mg/kg/h		38±9		28.26%					
Zeeni et al.	Lebanon	db rct	Laparoscopic bariatric	27	29	N/A		42.14+/-6.13	41.78+/-5.86	IVI Dex1mcg/kg IVI Dex 0.5 mcg/kg/h	IVI Morphine 0.08 mg/kg/10 min	38.04 ± 12.43	38.03± 10.44	Not stated	Not stated =	100.15±25.23	103.72±24.36	108.52±24.83	110.28±22.66

Table II: Outcomes of interest extracted from respective selected trials [8-20]

Author	Drugs	Outcome													
		Incidence of PONV[n(%)]	NRS nausea	Rescue phenylephrine [n(%)]	Time to discharge from PACU	Safe extubation	Rescue antiemetic	Duration of surgery (mins)	Duration of anaesthesia (mins)	Dose	Postop opiod use	Volatile anaes use	Intraoperative fentanyl (mcg)	Pain score	Total intraop opiod
Abu Halaweh et.al.	dex (nausea) morphine dex (vomiting) morphine	8(26) 19(63.3) 3(10) 7(23.3)					5.7+-3.1			0.3mcg/kg/h	6.1±3.1 (morphine) 4.7±2.9	N/A	2mcg/kg (induction) 2mcg/kg		
Bakhamees et.al.	Dex Control	2(5%) 3(7.5%)				5.1+-0.7 7.5 +- 1.3		157 ± 29 155 ± 27		0.8ug/kg bolus 0.4mcg/kg/h	5±1.4 (morphine) 10.2±1.3	N/A propofol infusion	199.4±44.6 362.2±57.2	1H 3(2-4) 2H 2(1-3) 1H 6(5-8) 2H 5(2-5)	362.2+-57.2 199.4+-44.6
Elbakry et al.	DEX Control DEX Control	5(10%) nausea 15(30%) 3(6%) vomiting 14(28%)			43.43+-10.36 52.12+-9.66	19.56+-5.31 20.36+-4.34	8.31+-2.34 ondan 11.34+-1.36	104.14±31.36 102.45 ± 30.33		0.5 - 1ug/kg/h	5.36±3.14 (morphine) 10.35±2.41	N/A desflurane vs tiva	N/A		5.36+-3.14 (morphine) 10.35+-2.41

Table II: Outcomes of interest extracted from respective selected trials [8-20]

Author	Drugs	Outcome													
		Incidence of PONV[n(%)]	NRS nausea	Rescue phenylephrine [n(%)]	Time to discharge from PACU	Safe extubation	Rescue antiemetic	Duration of surgery (mins)	Duration of anaesthesia (mins)	Dose	Postop opiod use	Volatile anaes use	Intraoperative fentanyl (mcg)	Pain score	Total intraop opiod
Ibrahim et al.	OFA	18(35.3)			30.0 [25.0-35.0]	9.0[9.0-11.0]		40.5 ± 9.04	63.7±8.61	0.1ug/kg	10 (0-10) median IQR morphine	sevoflurane 1.5-2.0 minimum alveolar concentration			
	MMA	24(46.2)			20[20.0-25.0]	5.5[4.0-9.5]		43.0±9.86	64.8±9.19	0.5ug/k/h	10 (10-20)	sevoflurane 1.5-2.0 minimum alveolar concentration	1mcg/kg (induction)		
Mostafa et al.	Dex	4(13%) nausea				5.8+-1.39		91.33±57.64	108.67±14.1	1ug/kg	43±15.12 (ketorolac)	sevoflurane 2-3%	178.33±25.2		178.33+-25.2
	Control	7(23%)				5+-1.73		85.07±12.4	101.9±15.69	0.5ug/kg/h	75.5±15.26	sevoflurane 2-3%	217.24±27.6		217.24+-27.6
	Dex	0 vomiting													
	Control	1(3.33%)													
	Dex	0 nausea and vomiting													
	Control	2(6.66%%)													
Naja et al.	dex	13(52)						126.03±24.6	171.5±27.6		337.50+-85.3(perop)	sevoflurane 1-1.5%	337.5±85.3	2.09+-1.9	337.5+-85.3
	clonidine	9(37.5)						138.01 ± 38.1	182.3 ± 39.9	0.5-0.8 ug/kg/h	371.71 +-73.9 (perop)	sevoflurane 1-1.5%	371.71 ± 73.9%	3.38+-2.8	371.71+-73.9
Narejo et.al.	dex	1 (5%) PACU			47.35 + -8.56	2.75 + -1.48	0.5+-2.24 meto	74.6 ± 23.19			3.7 ± 2.68 (morphine)	desflurane MAC 0.7-1%	2 mcg/kg (induction)	4.26 ± 1.97	
	remifentanil	6 (30%)			51.8 + -8.33	5.55 + -2.52	2.0 +-4.10	63.25 ± 16.18		0.2-0.7ug/k/h	3.0±3.58	desflurane MAC 0.7-1%	2 mcg/kg (induction)	4.15 ± 1.93	
	ex remifentanil	3 (15%) Ward 13 (65%)													
Sabra. et al.	Dex	2 (5.6%) nausea	34.22 ± 10.48				2.33 +-2.93 ondan	121.5 8± 33.7	174.47 ± 36.2	1 ug/kg	74.44 ± 12.29 (tramadol)	sevoflurane 1.0-2.5%	50.42±13.96	4.26 ± 1.97	50.42 ± 13.96
	Control	8 (22.2%)	62.5 ± 13.34				3.58+-2.68	138.2 ± 22.23	153.92 ± 33.3		89.89 ± 15.08	sevoflurane 1.0 2.5%	88.89 ± 25.83	4.15 ± 1.93	88.89 ± 25.83
	Dex	2 (5.6%) retching													
	Control	5 (13.9%)													
	Dex	1 (2.8%) vomiting													
	Control	6 (16.7%)													
	Dex	5 (13.9%) overall													
	Control	19 (53.8%)													
	Dex	34.22 ± 10.48													
	Control	62.5 ± 13.34													
Salama et al.	Dex	1	2.3+/-0.5 1(0-10points)					117.77±5.98			15.07 ± 2.65 (morphine)	sevoflurane 2%	134.17 ± 36.84		134.17 ± 36.84
	Control	10	2.0+/-0.5					117.87 ± 6.54		0.4 ug/kg/h	45.93 ± 4.56	sevoflurane 2%	254.17 ± 42.59		254.17 ± 42.59
Sherif & Elsersy	dex	20(40)	0.5±0.7 (4point) 0-none 1-nausea no vomiting 2-vomiting 3-severe persistent vomiting							1 ug/kg	14 ± 4 (morphine)	sevoflurane 2%	14 ± 15	186 ± 2 QoR	14 ± 15* (10-19)
	xlocaine	30 (61)	0.9±0.8							0.4 ug/k/h	18 ± 4	sevoflurane 2%	26 ± 16	173 ± 6	26 ± 16* (21-30)
	control	39 (79)	1.3±0.8								29±5	sevoflurane 2%	56 ± 17	140 ± 6	56 ± 17 (51 61)

Table II: Outcomes of interest extracted from respective selected trials [8-20]

Author	Drugs	Outcome													
		Incidence of PONV[n(%)]	NRS nausea	Rescue phenylephrine [n(%)]	Time to discharge from PACU	Safe extubation	Rescue antiemetic	Duration of surgery (mins)	Duration of anaesthesia (mins)	Dose	Postop opiod use	Volatile anaes use	Intraoperative fentanyl (mcg)	Pain score	Total intraop opiod
Tufanogullari et al	0.2	6 (31)	arrival in PACU 1±1* 30 min 1±2* 60 min 2±3	2(10)	81+-33	5+-3		110±62	145±63		113 ± 85 (fentanyl)	N/A (end tidal concentration only)	N/A	5 2	
	0.4	6 (31)	arrival in PACU 2±3 30 min 1±2* 60 min 1±2*	4(20)	82 +-24	6+-4		107 ± 35	143±51	0.2-0.4 ug/kg/h	108 ± 67			5 3	
	0.8 control	11 (57) 16 (84)	arrival in PACU 1±2 30 min 1±2* 60 min 1±3 arrival in PACU 3±3 30 min 3±3 60 min 3±3	10(50)* 4(20)	87 +-24 104+-33	9 +-6 7+-3		111 ± 56 116±52	145 ± 55 153 ± 54		120 ± 78 187 ± 99			4 3 6 3	
Zeeni et al.	DEX		PACU 2.5 [0-7] 60 min 2.5 [0-5] 24 hours 2 [0-6.75]		78.37 ± 27.10	108.52 +-24.83		100.15 ± 25.23	108.52±24.83	1ug/kg	12.22±5.54 (morphine)	sevoflurane 2%	2 mcg/kg (induction)	6[4-8.25]	1.63 ± 0.77 (remifen)
	Morphine		PACU 3 [0-7] 60 min 0.5 [0-4.75] 24 hours 3 [3-7]		76.62 ± 19.92	110.28+-22.66		103.72 ± 24.36	110.28±22.66	0.5ug/kg/h	23.48 ± 6.22	sevoflurane 2%	2 mcg/kg	7[3.5-9.5]	1.92 ± 0.77
Ziemann et al.	TIVA	12 (20%)		13 (21.7%)	44+-19			131 ± 69	195±73	0.5 ug/kg	2.29 ± 1.52 hydromorphe	infusion propofol seveoflurane MAC 0.7-1.3	0.5-1 mcg/kg (induction)		
	Classic	22 (30.5%)		18 (30.5%)	44+-23			118 ± 50	175±57	0.1-0.3 ug/kg/h	2.08 ± 1.17				

Table III: Summary of outcomes

Outcomes and subgroup analysis	Included studies	Result
3Incidence of PONV		
Incidence of PONV based on drug classes	12	Reduction in the incidence of PONV with use of DX (RR = 0.48 [0.41, 0.57]; p < 0.00001)
DX and duration of surgery	10	Significant reduction in the incidence of PONV with the use of DX if the duration of surgery was less than 120 minutes. (RR = 0.38 [0.26, 0.57]; p < 0.00001)
IV bolus DX prior to IV DX infusion.	11	Risk reduction without IV bolus DX prior to an infusion (RR = 0.42 [0.25, 0.71]; p = 0.001) was more compared to those with IV bolus DX (RR = 0.51 [0.40, 0.65]; p = < 0.0001).
Gender preponderance	11	Risk of PONV was reduced in DX group, without significant difference for the subgroup analysis between male >30% and <30%.
Numerical Rating Scale (NRS) of PONV		
NRS of PONV with DX versus other antiemetics	5	DX significantly lowered the risk of PONV compared to other groups. (SMD = -2.33 [-2.94, -1.73]; p = 0.0001)
Duration of surgery	4	DX significantly lower the risk of PONV in duration of surgery <120 minutes compared to >120 minutes of surgery. (SMD -1.28 (-2.30, -0.25)
IV bolus DX prior to IV DX infusion	2	
Gender preponderance	4	NRS of PONV is significantly lower in groups of < 30% male participants compared to >30% male participants. (SMD = -0.97 [-1.32, -0.62], p <0.00001) vs (SMD = -01.53 [-3.09, 0.04], p = 0.06)
Total dose of postoperative analgesia used		
DX versus other antiemetics	6	DX was shown to reduce the total postoperative analgesia requirement (SMD = -1.87 [-3.31, -0.42], p = 0.01) only significantly lowered when comparing DX to placebo (SMD = -4.04 [-6.99, -1.09]). No difference in SMD was noted when DX was compared to dexamethasone and opioid
IV bolus DX prior to IV DX infusion.	6	
Time to discharge from post-anaesthesia care unit (PACU)		
DX versus other antiemetics	5	DX significantly reduced the time to discharge from the PACU (SMD = -0.36 [CI -0.57, -0.15], p = 0.001). On subgroup analysis, DX only showed a significant reduction in the time to discharge from PACU when compared to placebo.
Total intraoperative opioid used		
DX versus other antiemetics	8	The use of DX intra-operatively did not affect the total amount of intraoperative opioid consumption (SMD = -1.14 [-2.47, 0.19]; p = 0.06).
IV bolus vs no bolus DX prior to infusion	8	An IV bolus dose of DX did not affect the total intraoperative opioid consumption
Time to safe extubation		
DX versus other antiemetics	6	No difference in the time to safe extubation with DX compared to other drugs.
IV bolus vs no bolus DX prior to infusion	6	Significant reduction in the time to extubation in the subgroup without a bolus dose (SMD = -1.73 [-1.31, - 0.33], p = 0.02).

Even though high subgroup heterogeneity was detected, the total heterogeneity was low (Figure 16).

Time to Safe Extubation

Seven trials reported data on time taken for safe extubation. One study was excluded from analysis as the result was reported in the median and interquartile range. Pooled analysis revealed no difference in the time to safe extubation with DX compared to other drugs. Nevertheless, subgroup analysis demonstrated a significant reduction in the time to safe extubation when DX was compared to opioids (SMD = -2.79 [-4.06, -1.52], p < 0.0001). High total heterogeneity and moderate subgroup heterogeneity were recognised (Figure 17).

When comparing the effect of bolus and no bolus before infusion of DX, the result revealed a significant reduction in

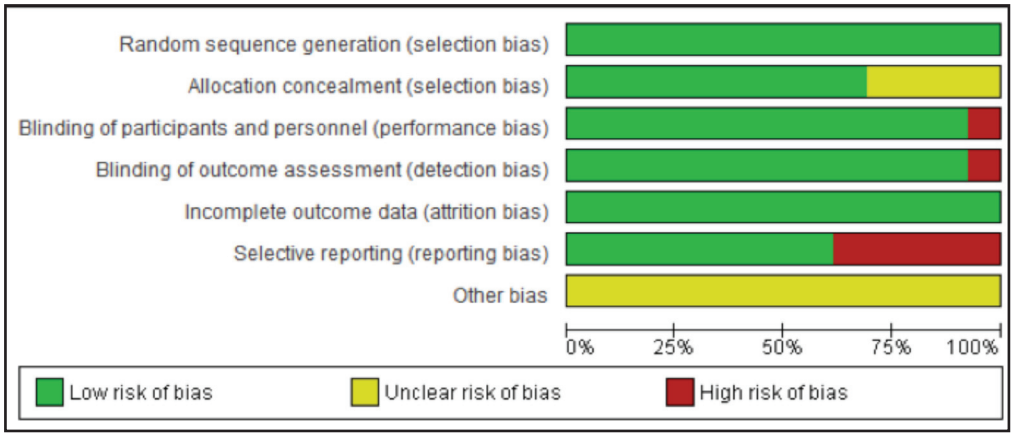

Fig. 1: Risk of bias graph.

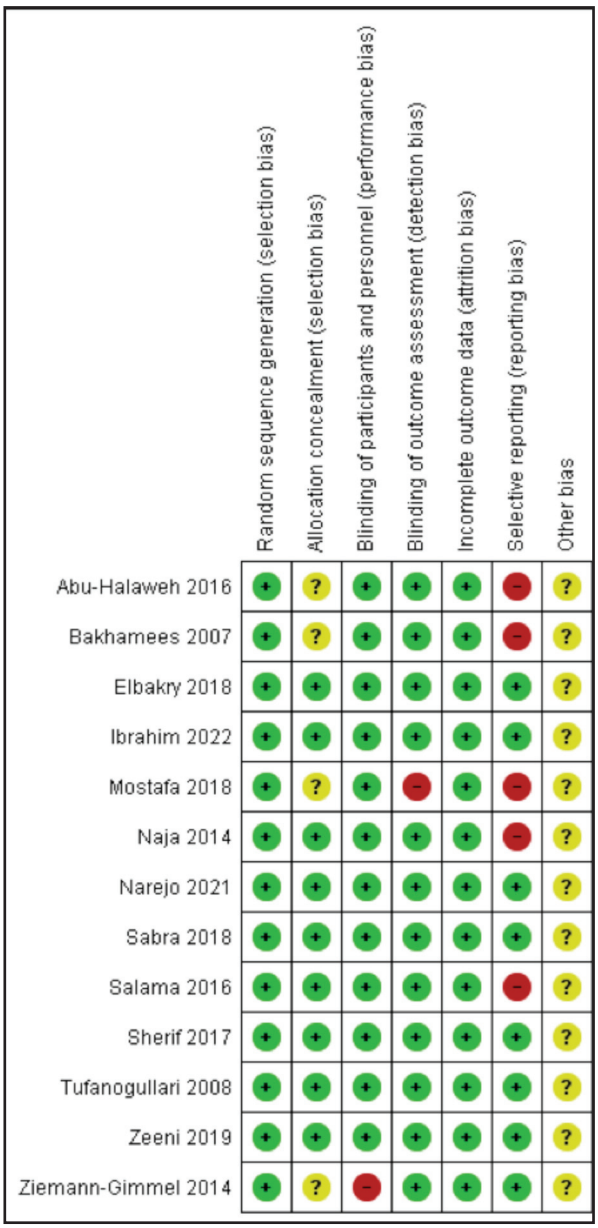

Fig. 2: Risk of bias summary

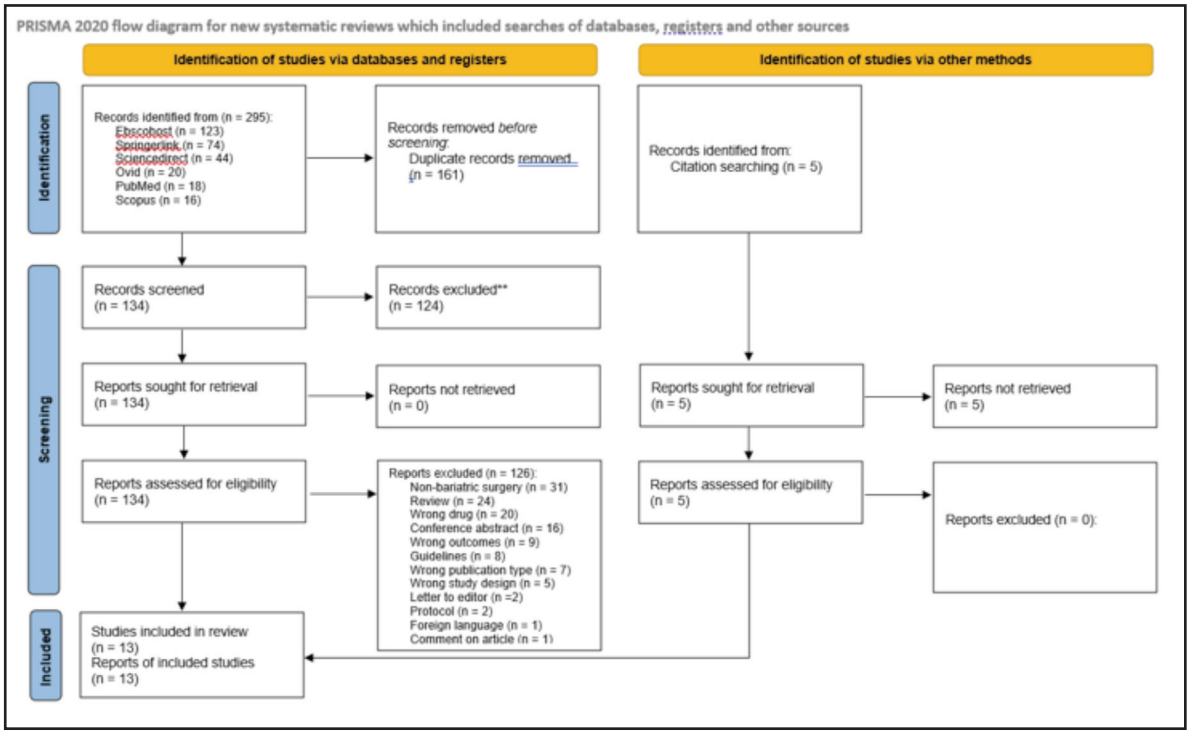

Fig. 3: Flow diagram using PRISMA flowchart

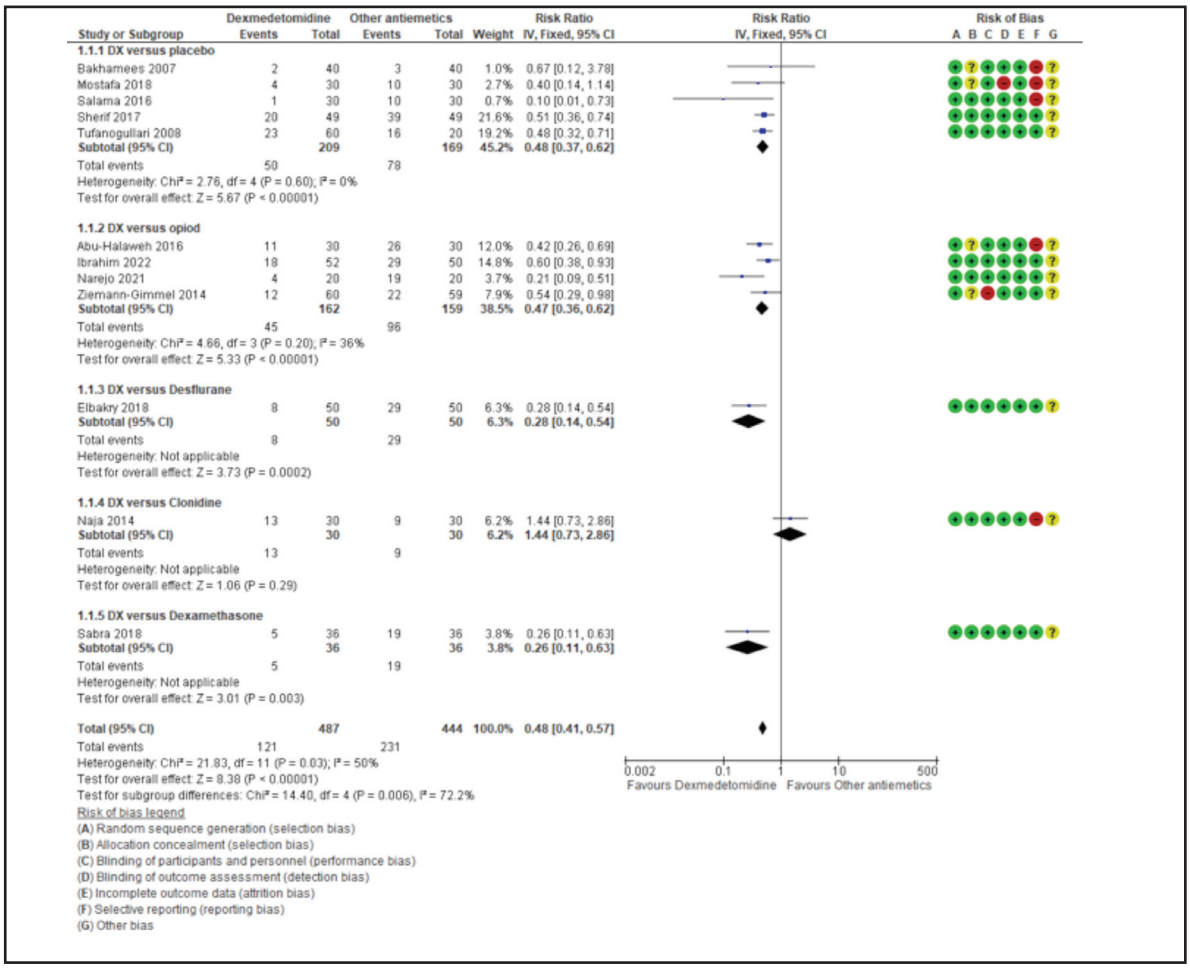

Fig. 4: Forest plot comparing the incidence of PONV of DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

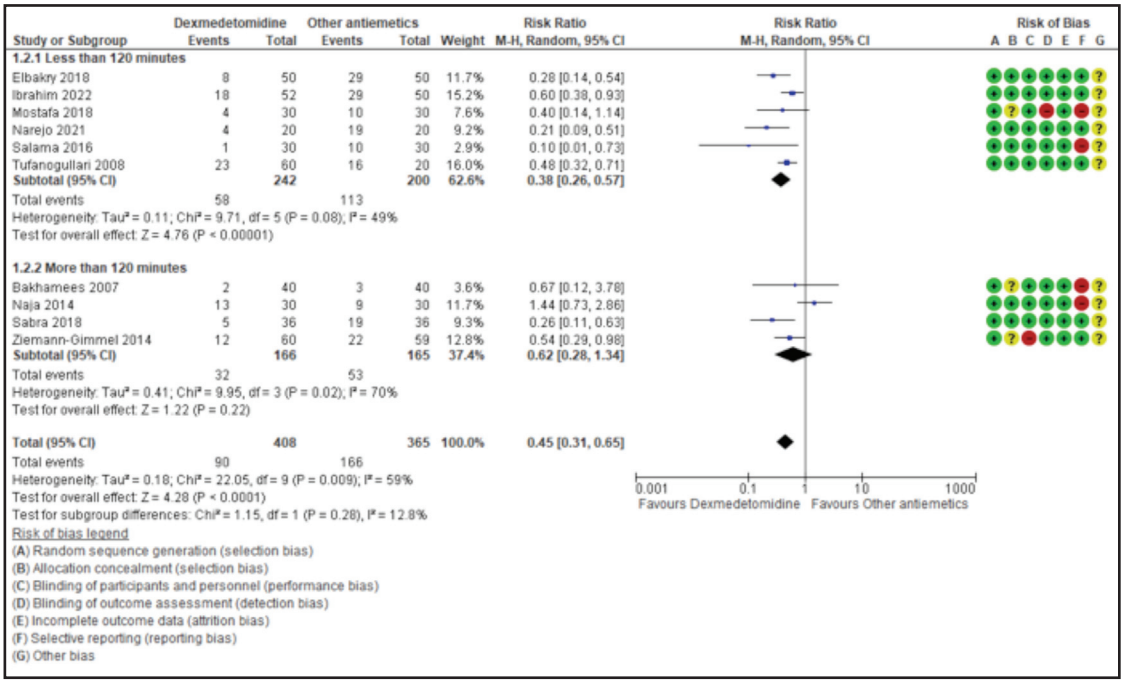

Fig. 5: Forest plot comparing the incidence of PONV with DX versus other antiemetics and subgroup analyses of duration of surgery.

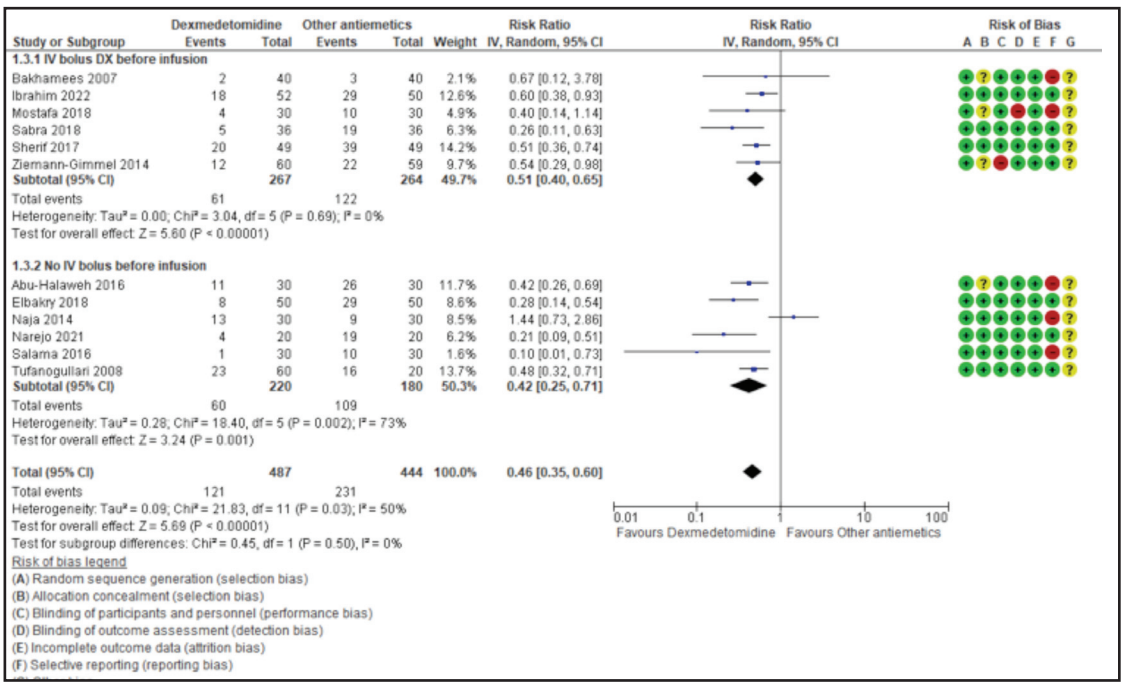

Fig. 6: Forest plot comparing the incidence of PONV with DX versus other antiemetics and subgroup analyses of administration of IV bolus and no IV bolus of DX before DX infusion.

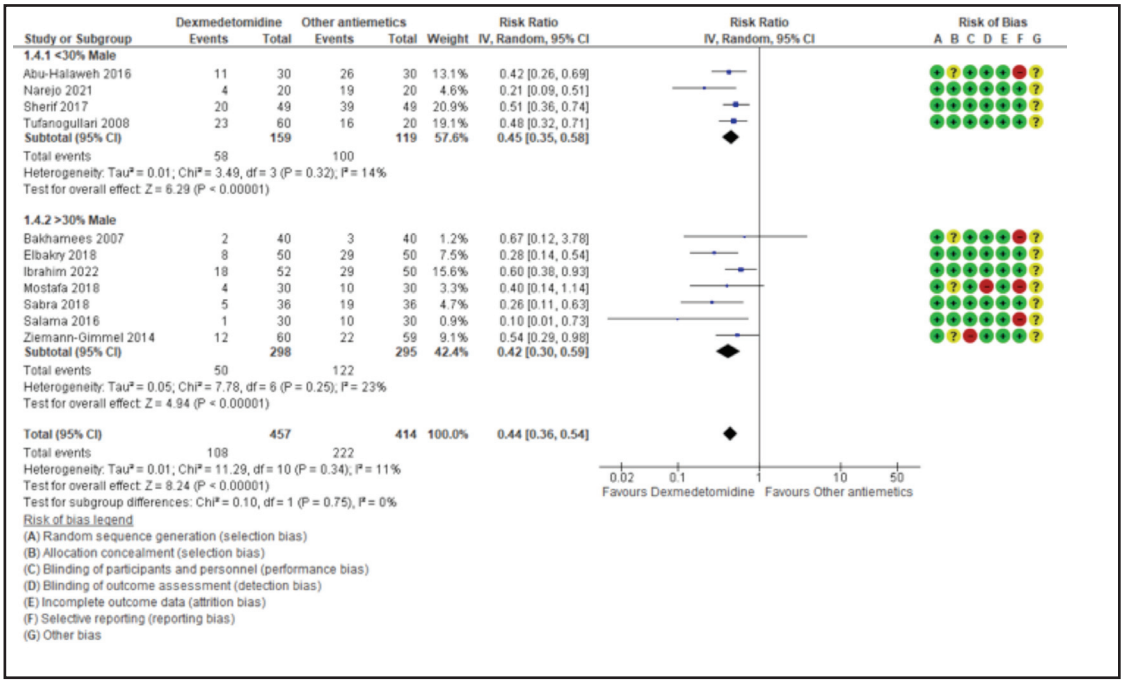

Fig. 7: Forest plot of incidence of PONV using DX versus other antiemetics and subgroup analyses of gender preponderance among participants.

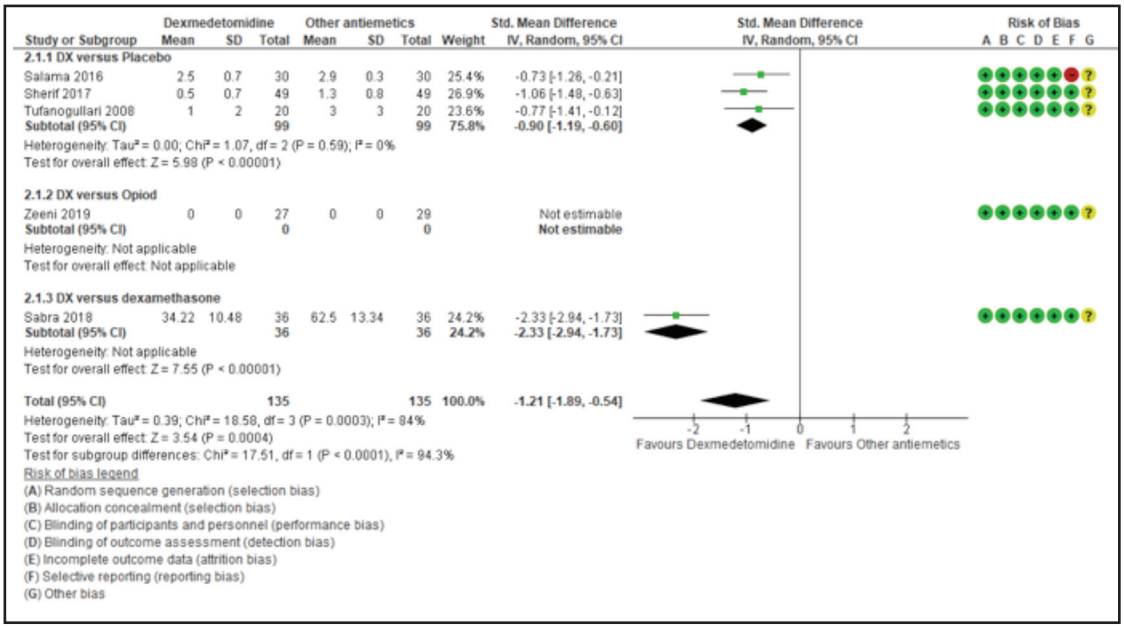

Fig. 8: Forest plot comparing the NRS scores of PONV using DX versus other antiemetics and subgroup analyses across various groups of antiemetics and opioids.

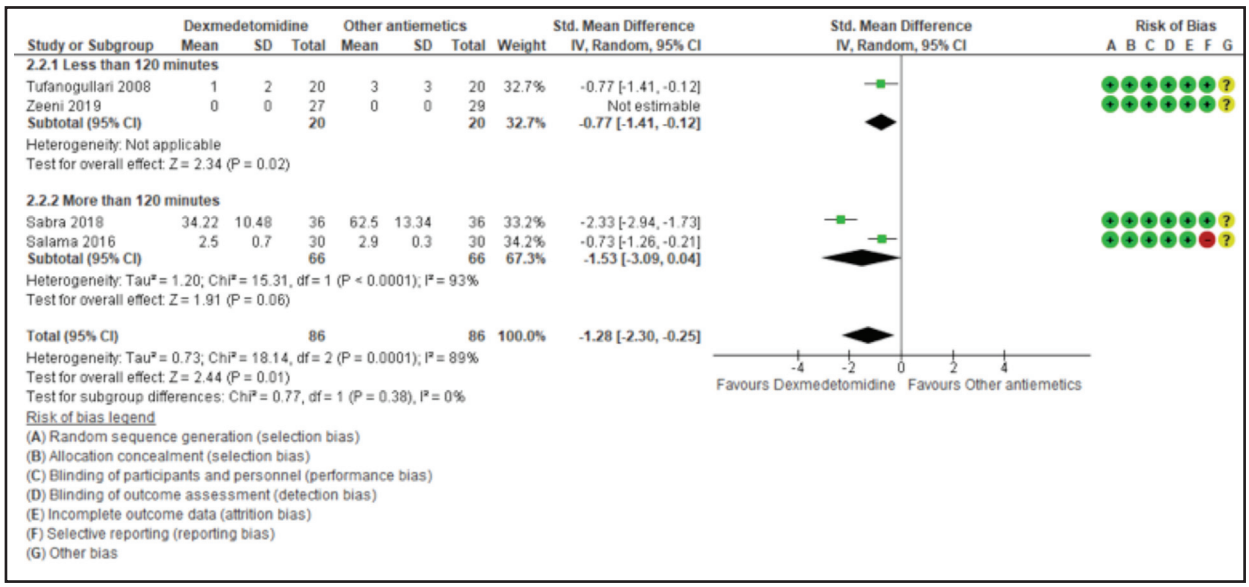

Fig. 9: Forest plot of comparison: NRS of PONV of DX versus other antiemetics and subgroup analyses of duration of surgery.

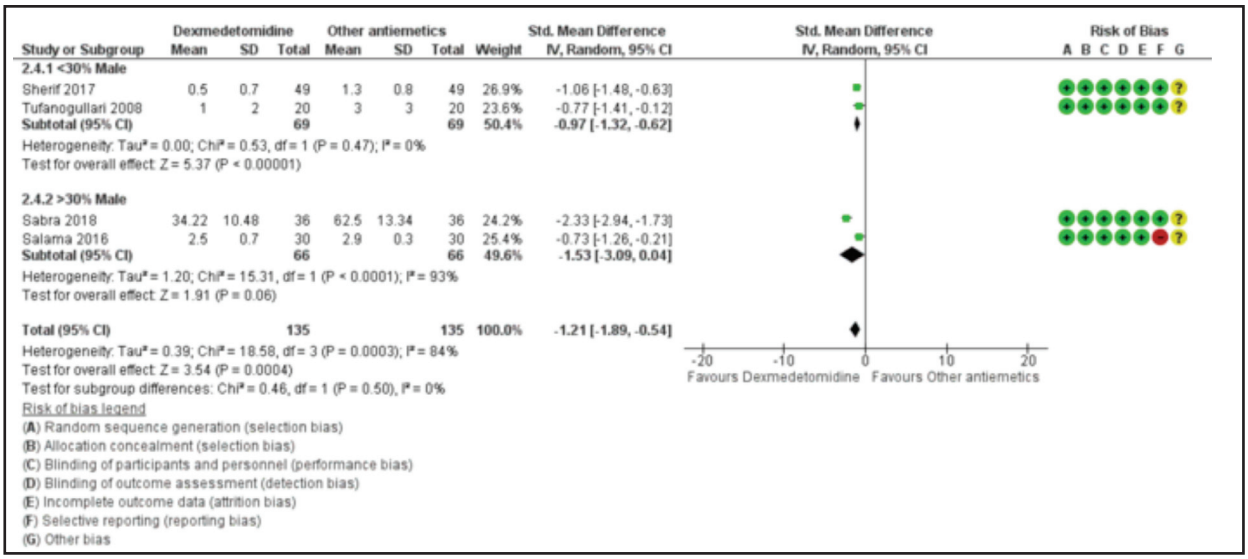

Fig. 10: Forest plot of comparison: NRS of PONV of DX versus other antiemetics and subgroup analyses of duration of surgery.

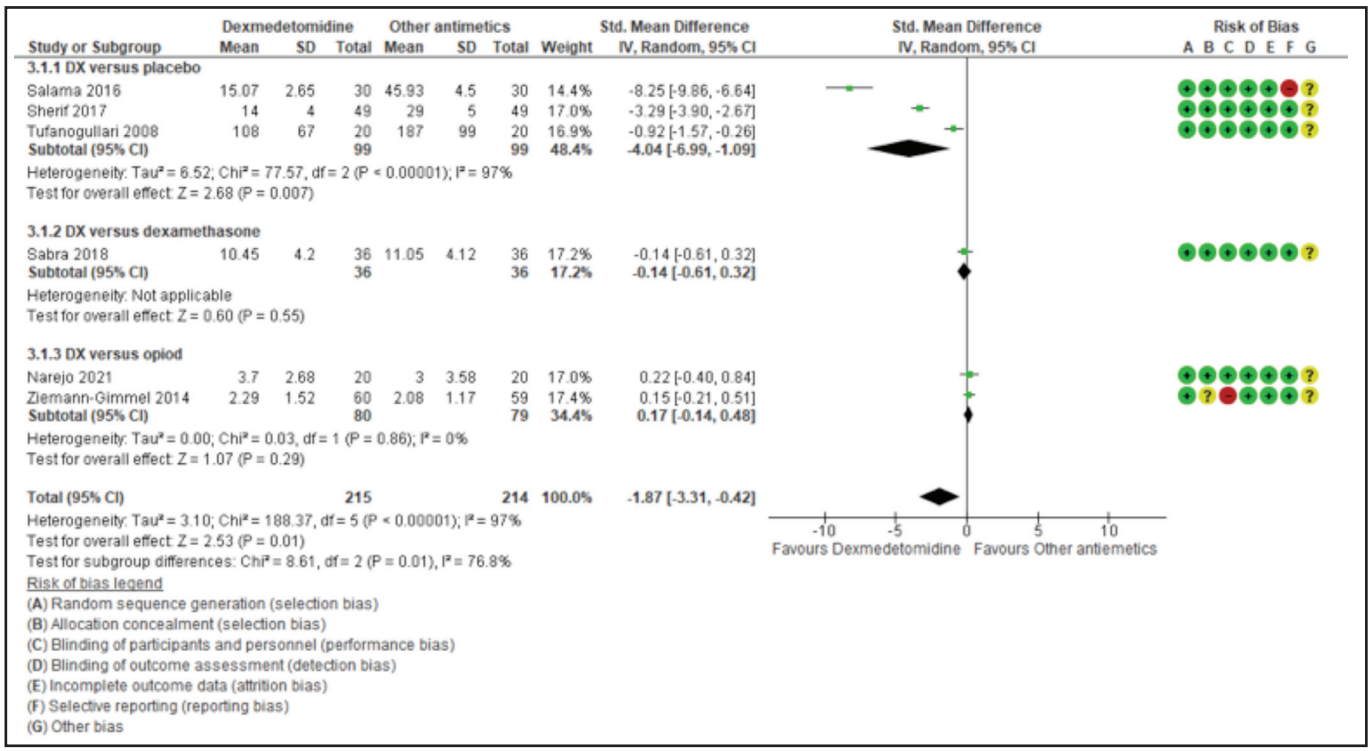

Fig. 11: Forest plot comparing total dose of postoperative analgesia used with DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

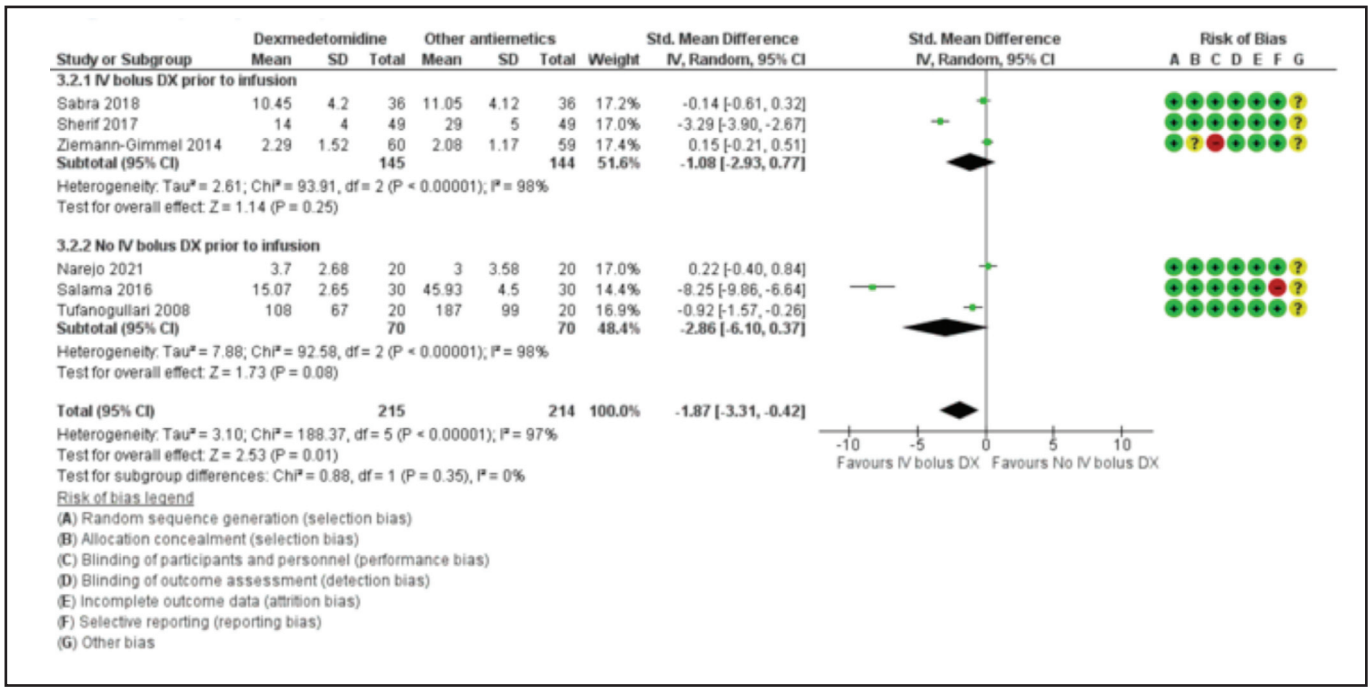

Fig. 12: Forest plot comparing total dose of postoperative analgesic used with DX versus other antiemetics and subgroup analyses of administration of IV bolus DX before IV DX infusion.

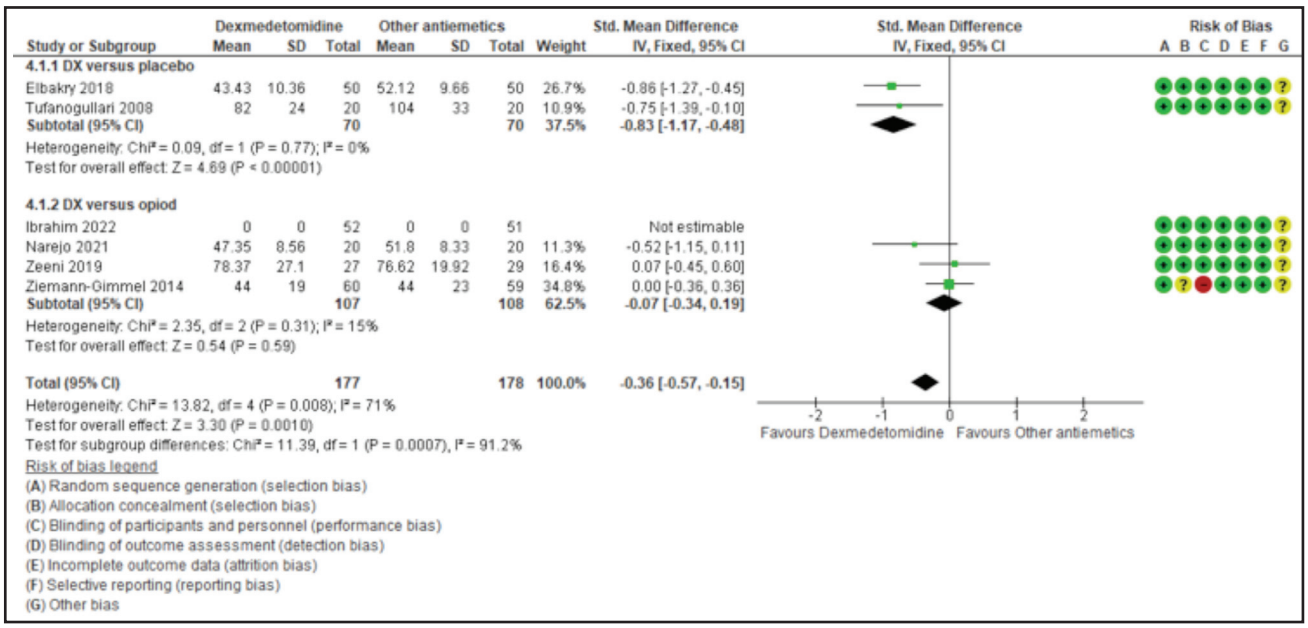

Fig. 13: Forest plot comparing time to time to discharge from PACU with DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

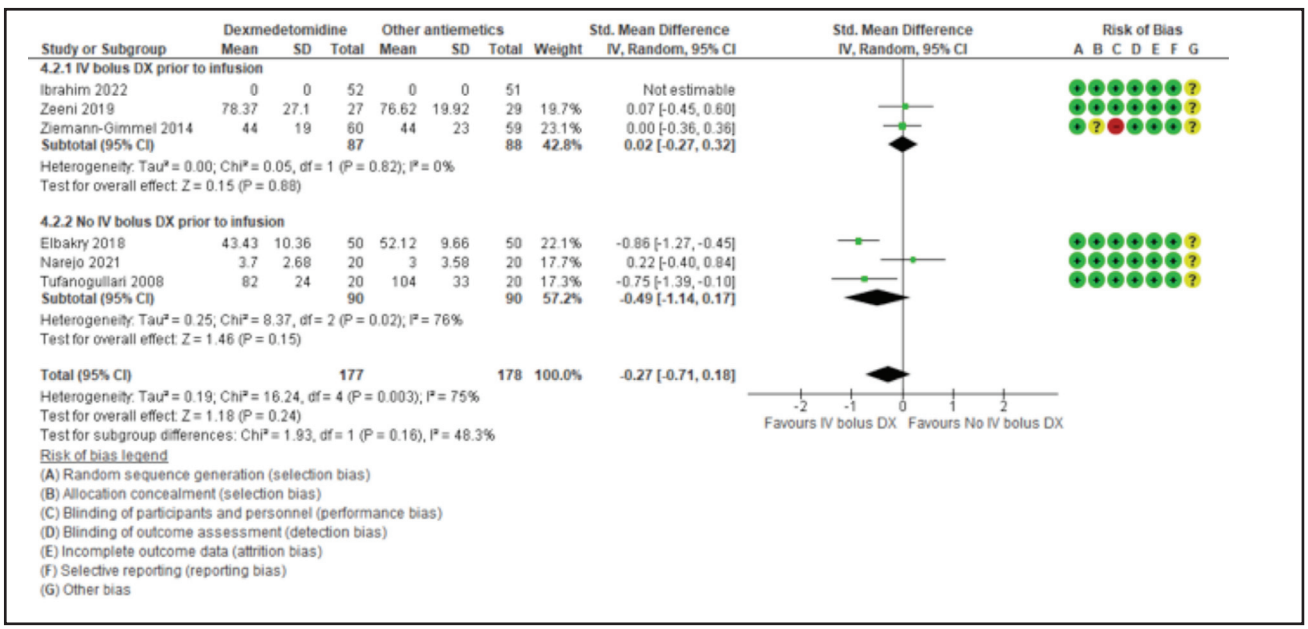

Fig. 14: Forest plot comparing time to discharge from PACU with use of DX versus other antiemetics and subgroup analyses of administration of no IV bolus and IV bolus of DX before initiating IV DX infusion.

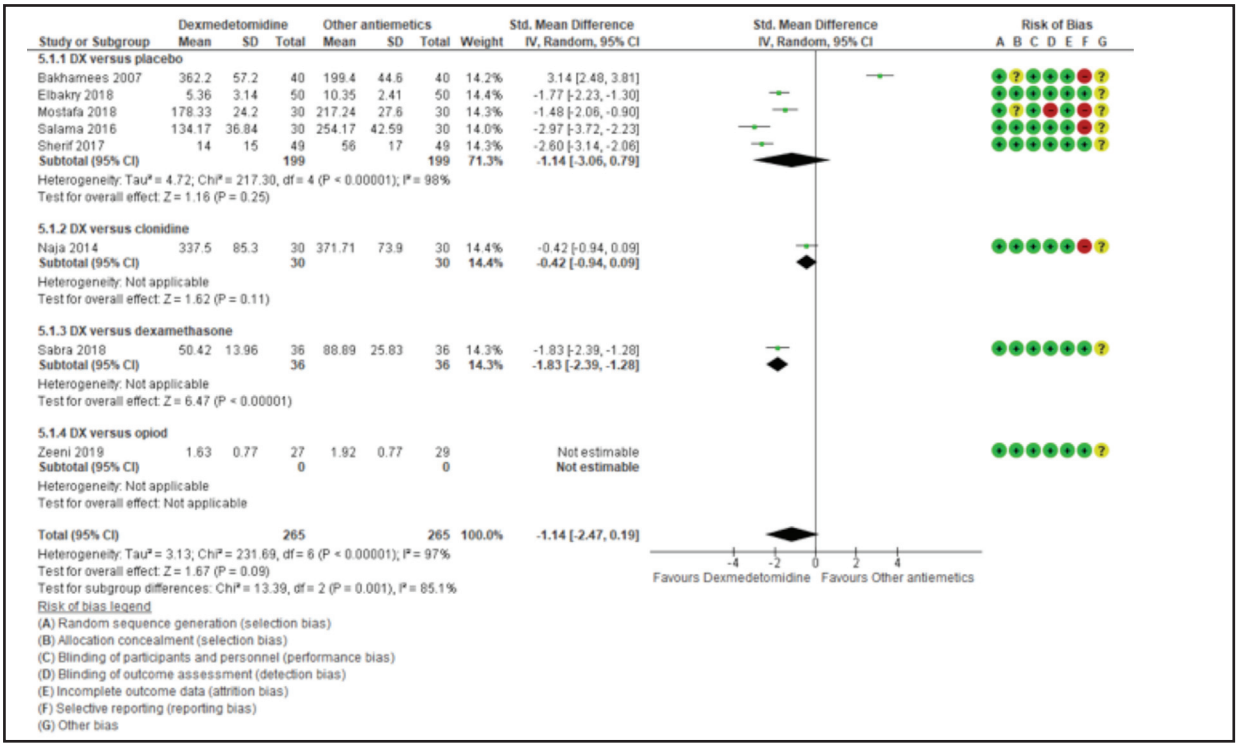

Fig. 15: Forest plot comparing DX versus other antiemetics and subgroup analyses across various groups of drugs in terms of total intraoperative opioid utilisation.

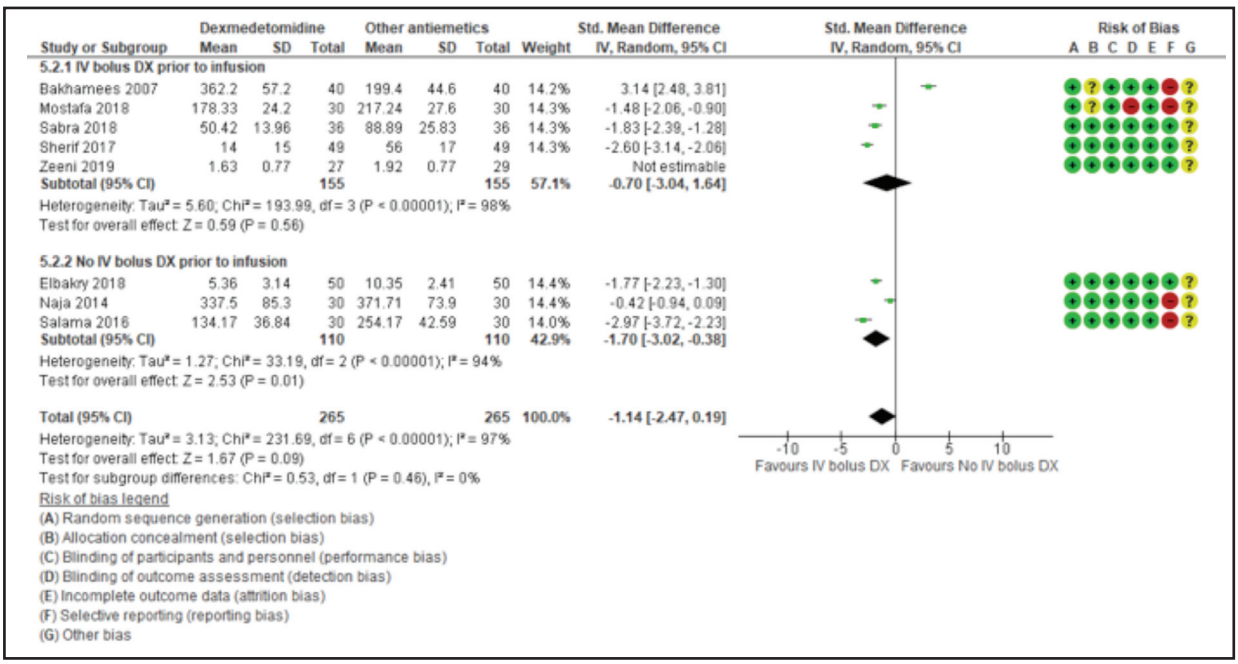

Fig. 16: Forest comparing total intraoperative opioid use with DX versus other antiemetics and subgroup analyses of administration of IV bolus DX before IV DX infusion.

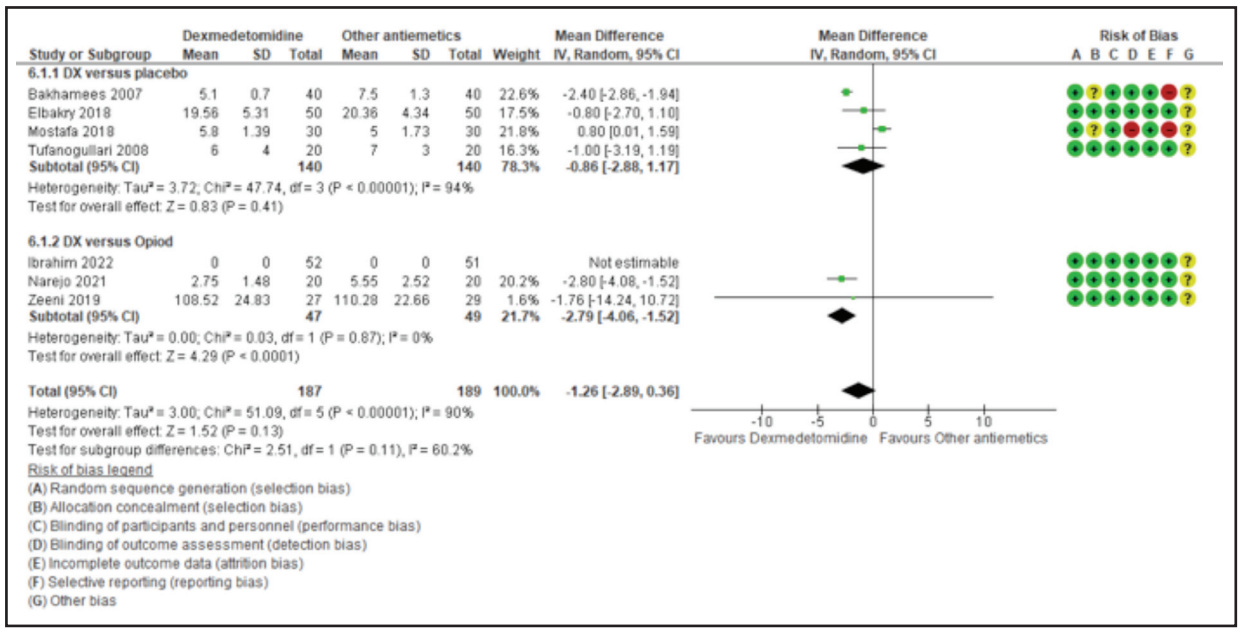

Fig. 17: Forest plot comparing time to safe extubation using DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

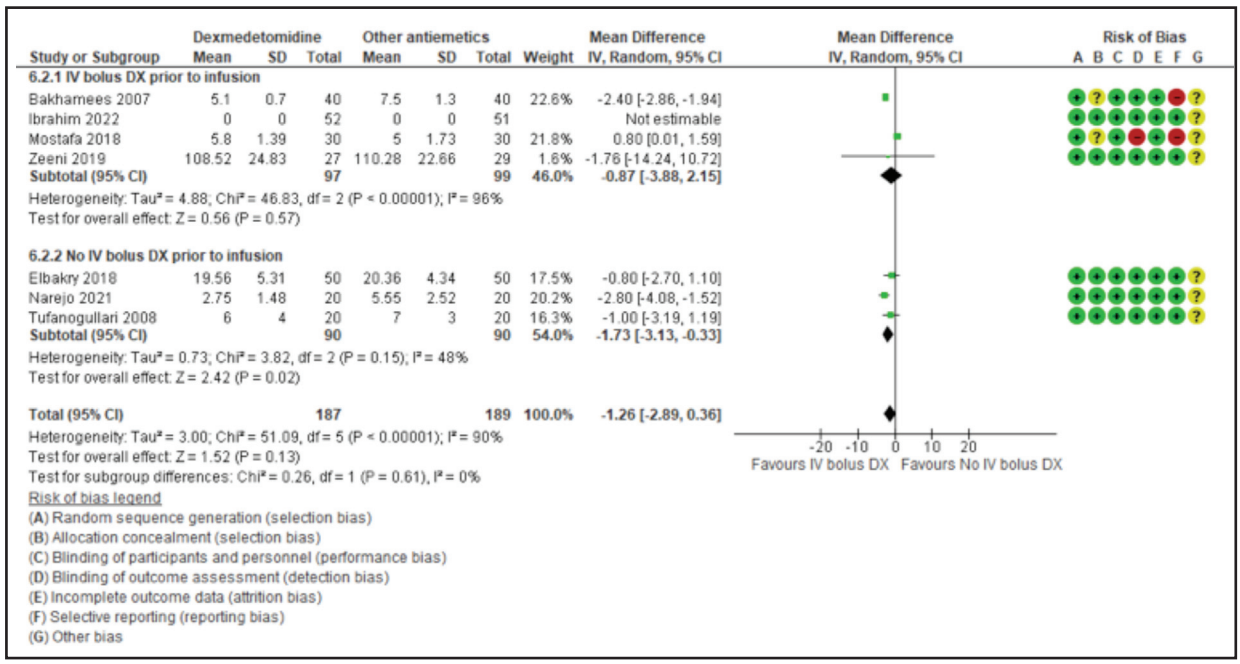

Fig. 18: Forest plot comparing time to safe extubation with DX versus other antiemetics and subgroup analyses of application of IV bolus to no bolus DX before DX infusion.

the time to extubation in the subgroup without a bolus dose (SMD = -1.73 [-1.31, - 0.33], p = 0.02). No subgroup difference was identified despite a high total heterogeneity.

DISCUSSION

Some of the risk factors that have been established to demonstrate a positive association with PONV are female gender, past history of PONV, use of volatile anaesthetics, nitrous oxide, and amount of postoperative opioids.[6] Even though the association of BMI as a risk factor for PONV remained debatable, laparoscopic bariatric surgery has been conclusively proven to have a high rate of PONV.[6,21-23] This is an important issue to be addressed as vomiting may lead to complications such as aspiration pneumonia, wound dehiscence as a result of increased intraabdominal pressure, oesophageal rupture, electrolyte, and fluid imbalance, which may lead to increased incidence of hospital readmission, longer hospital stay, and higher healthcare expenditures.[24] Current guidelines on PONV are not specific for bariatric surgery, but a multimodal pharmacologic approach is encouraged as prophylaxis for patients at high risk of PONV. This meta-analysis demonstrated that the incidence of PONV was significantly reduced after administration of DX. This result was similar to other studies on the use of DX in gynaecological, abdominal, breast, paediatric strabismus, nasal surgeries, and post-craniotomy.[25-28] This was found to be more pronounced in surgeries that lasted < 120 minutes, as a shorter time for surgery also meant reduced exposure to volatile anaesthetics and lower doses of opioids which are major risk factors for PONV.

Furthermore, the analgesic effect of DX as suggested by many studies (Figure 12) reduced the total amount of postoperative opioid requirement, thus reducing the incidence of opioid-related adverse effects, particularly nausea and vomiting.[26,29,30] One would expect the analgesic effect of DX to reduce the total intraoperative opioid use, and this was seen in the studies by Le Bot et al. and Jin et al. in various types of surgeries including neurosurgery, gynaecology, ophthalmology, and others. In contrast, in our study, subgroup analysis did not show a significant difference in the total dose of intraoperative opioids administered (Figure 16).[30,31] It is worth noting that there was high heterogeneity in the results due to several reasons. Firstly, the anaesthetic regimen widely differed from one another, for instance, Salama et al.[19] prescribed PO 75 mg pregabalin before surgery, while Ziemann et al[11] administered a single dose of IV ketamine 0.5 mg/kg. These medications may have influenced the total dose of opioids used by the anaesthetist during the surgery. Secondly, the duration of surgery as mentioned before, ranged from 40 minutes up to 150 minutes, which would also significantly alter the requirement of intraoperative opioids. Most of the included studies aimed to investigate the analgesic effect of DX and some studies compared the analgesic effect of DX to a variety of opioids resulting in greater expectation of significant differences in results related to opioids.

We found that NRS demonstrated a significant difference in scores for PONV with reduced incidence of PONV. This indicates that DX was able to reduce severity and the incidence of PONV. This was probably due to the intrinsic effect of DX whereby the sympatholytic effect of α2-adrenergic receptor agonist reduces plasma concentration of catecholamine, a known attributing factor of PONV, as well as the analgesic-related effect discussed in the earlier section.[30,32] Similarly, the severity was only markedly reduced if the surgery lasted < 120 minutes. The result was subjected to high total and subgroup heterogeneity which may be due to a few factors. Firstly, the lack of a standardised scoring system caused by use of different scale systems in various studies for example, the 11-point VRS scale by Tufanogullari et al,[8] 4-point scale by Sherif and Elsersy[9] and the visual analog score (VAS)of 100 points used by Sabra et al.[18] Secondly, Wilkstrom et al.[33] found that although NRS correlates to patients' verbal scale, there was only moderate correlation to their retrospective reported experience. This meant that NRS might suffer from subjectivity and patients' perspectives and be sensitive to changes in other factors such as small fluctuations in symptoms and complexity in translating the exact severity into scores. Besides that, premedication i.e., with ondansetron, which was given in some trials may have affected the overall NRS. Lastly, the documentation interval of NRS varied across different trials, which may have affected the overall analysis of the results.

The significant reduction in the mean NRS for PONV was most obvious when DX was compared with dexamethasone. Multiple studies identified dexamethasone as an efficacious prophylactic agent for PONV.[26,34-36] The combination of single dose IV DX 1ug/kg, dexamethasone 8 mg, and ondansetron 4 mg in the intervention group in one of the studies, suggested promising antiemetic results when combining DX and dexamethasone. Our findings were in discordance with the affirmation.[37] (Figure 8) Up to date, there are insufficient trials available that focus on the synergistic effect of DX and dexamethasone, hence more studies are needed to affirm the efficacy of this combination.

It appears that administering a loading dose of DX before starting infusion will not make a difference in terms of PONV as a continuous infusion was sufficient to significantly, lower the incidence and NRS of PONV. This result was similar to a study by Jin et al.[30] In addition, with these two ways of administering the DX, there was no effect on the total intraoperative and postoperative opioid consumption. In contrast, a loading dose of DX may raise the concern of a higher incidence of adverse effects of DX such as hypotension and bradycardia.[8,30,38] Therefore, DX as a continuous infusion without a loading dose appears safer and more effective.

All the included trials did not report the incidence or NRS of PONV based on gender. As mentioned earlier, female gender is one of the strongest predictors of PONV.[6] Since the exact numbers of participants based on gender were unavailable, subgroup analysis was done based on the proportion of male to female participants in the study. The benchmark was set to be 30%. A group with < 30% male was considered female-predominant, therefore, a higher incidence and NRS of PONV were expected. Overall, both groups responded to DX and there was a significant reduction in NRS in the female-predominant group, suggesting that females responded better to DX than males.(Figure 10)

The use of IV bolus and no bolus before initiating infusion of DX during induction did not influence the time to discharge from PACU and no significant difference was noted when DX was compared to opioids. Subgroup analysis of DX versus placebo and opioid respectively, DX only showed a significant reduction in the time to discharge from PACU when compared to placebo. There were high subgroup differences and moderate total heterogeneity. This could be secondary to other factors like pain scores, sedation, and vital signs that may influence the time to discharge from PACU. Future research specifically targeting DX, other anti-emetics, and factors affecting the stay in PACU before discharge may address this limitation.

A review of the data obtained from the included articles revealed a lower mean arterial pressure in the group administered with dexmedetomidine which is in accordance with previously determined side effects of dexmedetomidine.[39] Data on the average heart rate of the patient and respiratory depression were not clear from most of the included studies. However, the cardiopulmonary effects following dexmedetomidine infusion were determined in the research by Deutsch et al., where results showed a lowered heart rate in patients but no significant respiratory depression.[40] The increased risk of PONV in morbidly obese who are also sensitive to opioids and laparoscopic surgery may be a reason to explore DX as a drug of choice for this population of patients. However, current RCTs do not explore the side effects of dexmedetomidine use enough, and more data should be obtained regarding the safety profile of the medication to be used as prophylaxis for PONV.

Limitations

Most of the included studies reported the efficacy of DX from many aspects of outcomes. Incidence of PONV was available in most of the studies but not all. Additionally, the type of NRS, use of opioids, and timing of administration were different. This could be a primary limitation of our report.

Secondly, we are aware that the incidence of reduction of PONV could be affected by the use of opioids. Thirdly, outcomes such as time to discharge from PACU could be confounded by other factors such as comorbidity, pain score, currently taking medications, etc. Lastly, this population's limited number of RCTs may have affected our analysis.

CONCLUSION

From this analysis, there is considerably sufficient evidence to prove that the administration of dexmedetomidine (DX) can reduce the incidence of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic bariatric surgery. The increased risk of PONV in morbidly obese who are also sensitive to opioids and laparoscopic surgery may be a reason to explore DX as a drug of choice for this population of patients with or without dexamethasone.

We also found that the additional analgesic effects of dexmedetomidine reduce postoperative opioid requirements, which can contribute to reducing the incidence of PONV as well. The use of DX appeared to significantly reduce the incidence of PONV when the duration of surgery was < 120 minutes.

Future trials should focus on NRS and its correlation with PONV using DX in laparoscopic bariatric surgeries, and the antiemetic properties of DX in different doses and regimens should be explored.

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