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# Abstract

**Introduction** Today, the number of cesarean section has drastically increased. Newer scientific reports have shown Magnesium sulfate (MgSO4) to have favorable outcomes for anesthesia. In this analysis, we aimed to systematically compare the adverse drug events observed with intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section.

**Methods** MEDLINE, EMBASE, Web of Science, Google scholar, http://www.ClinicalTrials.gov, and the Cochrane database were searched for relevant publications comparing the adverse drug events observed with intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section. The RevMan software version 5.4 was used to analyze data in this analysis. Risk ratios (RR) with 95% confidence intervals (Cls) were used to represent analysis for the dichotomous data whereas weighted mean difference (WMD) with 95% Cl was used to represent results using continuous data. Heterogeneity was assessed by the Q statistic and the l2 statistic tests.

**Results** Eleven studies with a total number of 895 participants were included in this analysis whereby 466 patients were assigned to intrathecal MgSO4 and 429 participants were assigned to a control group. The main results of this analysis show that intrathecal MgSO4 as an adjuvant to bupivacaine was associated with a significantly lower risk of shivering (RR: 0.63, 95% CI: 0.48 – 0.83; P = 0.001). In addition, the risks for hypotension (RR: 1.11, 95% CI: 0.86 – 1.44; P = 0.40), nausea and vomiting (RR: 1.08, 95% CI: 0.76 – 1.54; P = 0.65), pruritus (RR: 0.77, 95% CI: 0.51 – 1.17; P = 0.22), and bradycardia (RR: 4.45, 95% CI: 0.97 – 20.36; P = 0.05) were not significantly increased. The sensory (WMD: 23.15,

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95% CI: 7.83 – 38.48; P = 0.003), and motor block duration (WMD: 24.29, 95% CI: 16.36 – 32.23; P = 0.00001) and the duration of spinal anesthesia (WMD: 29.24, 95% CI: 13.61 – 44.87; P = 0.0002) were significantly in favor of MgSO4.

**Conclusion** Intrathecal MgSO4 as an adjuvant to bupivacaine was associated with a significantly lower risk of shivering without causing any increase in other adverse drug events in patients undergoing elective cesarean section. Efficacy outcomes were also appreciated. Larger studies should be able to confirm this hypothesis.

**Keywords** Magnesium sulfate, Bupivacaine, Spinal anesthesia, Cesarean section, Adverse drug events, Shivering, Hypotension, Nausea and vomiting, Pruritus

# Introduction

Today, even though the total number of pregnancies has decreased, the number of cesarean sections has drastically increased [1]. Thirty three percent (33%) of the deliveries done in the United States [2] are by cesarean section whereas in China, the rate has climbed to up to 35% [3]. Unfortunately, inadequate pain management has shown to be one of the contributing factors for morbidity, delayed recovery, chronic pain and post-traumatic distress syndrome [4]. Therefore, newer interventions are now focusing on how to reduce pain post-operatively [5].

New scientific reports have shown Magnesium sulfate (MgSO4) to have favorable outcomes for anesthesia [6]. Several benefits including shortening of anesthetic induction, decrease total post-operative analgesic requirements, reduction in anesthetic requirements, maintaining favorable hemo-dynamics and significantly lowering maternal and neonatal adverse effects have been observed [7].

Two meta-analyses based on the impact of intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section have previously been published [8, 9]. However, both of the papers focused on post-operative analgesia only. No previous meta-analysis [8, 9] has yet reported adverse drug events following the use of intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section.

Therefore, in this analysis we aimed to systematically compare the adverse drug events observed with intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section.

## Methods

## Data sources, search strategies and searched terms

MEDLINE, EMBASE, Web of Science, Google scholar, h ttp://www.ClinicalTrials.gov, and the Cochrane database were searched for relevant publications comparing the adverse drug events observed with intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section.

Reference lists of selected articles were also verified for relevant publications.

The searched terms included:

- 'Magnesium sulfate, bupivacaine and cesarean section';
- 'Magnesium sulfate, bupivacaine and spinal anesthesia and cesarean section';
- 'Magnesium sulfate, spinal anesthesia and cesarean section'.

# **Criteria for inclusion**

Studies were included if:

- (a) They were based on intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section;
- (b) They reported adverse drug events with or without efficacy outcomes;
- (c) They included a control group;
- (d) They were published in English.

# **Criteria for exclusion**

Studies were excluded if:

- (a) They were reviews (systematic reviews, brief reviews, literature reviews);
- (b) They were meta-analyses, network analyses;
- (c) They did not report adverse drug reactions;
- (d) They did not include a control group;
- (e) They were published in a different language except English;
- (f) They were duplicated studies from the same trial.

### Data extraction, quality assessment and risk of bias

The authors independently extracted data after carefully assessing the selected studies. The total number of pregnant women who were assigned to MgSO4 and the control groups respectively, the adverse drug events and/ or the efficacy outcomes which were reported, the endpoints which were assessed, the type of study and the participants' enrollment time period, the gestational weeks, the body mass index, the weight and height of the participants as well as the type of participants, and the methodological features of the original studies were all carefully extracted. Any disagreement which followed during this data extraction process was carefully discussed among the authors and a consensus was finally reached.

The quality assessment of the trials was carried out based on the recommendations suggested by the Cochrane database [10]. This Risk of Bias (RoB) tool was used to assess the methodological quality of the trials. The bias assessment report was generated through the RevMan software.

### Statistical analysis

This is a meta-analysis and heterogeneity is obvious in such studies. The RevMan software version 5.4 (The Cochrane Collaboration, United Kingdom) was used to analyze data in this analysis. First of all heterogeneity was assessed by the Q statistic test whereby a p value less than 0.05 was considered significant statistically and a p value greater or equal to 0.05 was considered insignificant. Heterogeneity was also assessed by the I<sup>2</sup> statistic test whereby a subgroup analysis with an I<sup>2</sup> value less than 50% was considered to have a low heterogeneity and a subgroup analysis with an I<sup>2</sup> value greater than 50% was considered to have a low heterogeneity. A fixed effect statistical model was used for lower heterogeneity (I<sup>2</sup> < 50%) whereas a random effect statistical model was used for an increasing I<sup>2</sup> value.

Risk ratios (RR) with 95% confidence intervals (CIs) were used to represent data following analysis of dichotomous data.

For the continuous data, weighted mean difference (WMD) with 95% CI was used to represent the data. This was calculated using the mean, standard deviation and the number of participants in each related original study.

Sensitivity analysis was also carried out whereby each trial was excluded one at a time and a new analysis was carried out each time to verify for any significant change from the main results.

Publication bias was visually estimated through funnel plot which was generated by the Revman software.

### **Ethical approval**

Ethical approval was not required for this study. This study did not involve experiment on animals or humans carried out by any of the authors.

# Results

### Search outcomes

A total number of 109 publications were obtained through this search process which followed the PRISMA (Preferred Reporting Items in Systematic Reviews and Meta-Analyses) guideline [11]. After carefully reviewing the titles and abstracts, as well as going through the data given in the abstracts, irrelevant studies were eliminated and at last, 57 full texts articles were assessed for eligibility.

While going through the 57 full texts articles, further eliminations were carried out based on the following reasons:

- (a) Meta-analyses (2);
- (b)Adverse drug events were not reported (6);
- (c) Case studies (3);
- (d)Repeated studies obtained from different search databases (35).

Finally, only 11 studies [12-22] were included in this analysis. The flow diagram for the study selection has been illustrated in Fig. 1.

This Risk of Bias (RoB) assessment has been presented in Fig. 2.

All the studies had low risk of bias as shown in the Figure. The randomization sequence generation, the allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment were all well carried out and reported. Other bias was not reported in the studies.

### Endpoints to be assessed

This analysis involved patients who underwent elective cesarean section. The adverse drug events which were reported in the original studies have been listed in Table 1.

The endpoints which were studied included:

- (a) Shivering;
- (b)Hypotension;
- (c) Nausea and vomiting;
- (d) Pruritus;
- (e) Bradycardia.

The efficacy outcomes, which were also listed in Table 1, have also been assessed and included:

- (a) Sensory block onset time (minute);
- (b)Sensory block duration time (minute);
- (c) Onset of motor block time (minute);
- (d) Duration of motor block (minute);
- (e) Time to first request of anesthesia (minute);
- (f) Duration of spinal anesthesia (minute).

# General and baseline features of the studies and participants respectively

The general features of the selected studies have been listed in Table 2. Most of the studies which were included were prospective randomized studies which enrolled patients during years 2010 - 2015. A total number of 895 participants were included in this analysis whereby 466



Fig. 1 Flow diagram showing the study selection for this analysis

patients were assigned to intrathecal MgSO4 and 429 participants were assigned to a control group as shown in Table 2.

The baseline features of the participants have been listed in Table 3. The mean age of the participants was 23.0 to 35.0 years. The body mass index of the participants varied from 24.0 to  $29.7 \text{ Kg/m}^2$  whereas the mean gestational age varied from 36.0 to 39.0 weeks as shown in Table 3.

## Main results of this analysis

The main results of this analysis show that intrathecal MgSO4 as an adjuvant to bupivacaine in patients undergoing elective cesarean section was associated with a significantly lower risk of shivering (RR: 0.63, 95% CI: 0.48 - 0.83; p = 0.001) as shown in Fig. 3. In addition, the risks for hypotension (RR: 1.11, 95% CI: 0.86 - 1.44; p = 0.40), nausea and vomiting (RR: 1.08, 95% CI: 0.76 - 1.54; p = 0.65), pruritus (RR: 0.77, 95% CI: 0.51 - 1.17; p = 0.22), and bradycardia (RR: 4.45, 95% CI: 0.97 - 20.36; p = 0.05) were not significantly higher compared to the control group as shown in Fig. 3.

The efficacy outcomes were also reported. The sensory block duration as well as the motor block duration time were significantly in favor of intrathecal MgSO4 with (WMD: 23.15, 95% CI: 7.83 – 38.48; p = 0.003) and (WMD: 24.29, 95% CI: 16.36 – 32.23; p = 0.0001) as shown in Fig. 4. The duration of spinal anesthesia was also in favor of MgSO4 with (WMD: 29.24, 95% CI: 13.61 – 44.87; p = 0.0002). However, no significant difference



### Fig. 2 Risk of bias assessment

# Table 1 The endpoints which were reported

Studies	Efficacy outcomes	Adverse drug events reported	Type of surgery
Elsharkawy 2018 [12]	Time to reach T6 sensory block (minute), onset time of motor block (min- ute), time for complete motor block (minute), pain free period (minute), number of patients needing supplementary analgesics, total post opera- tive fentanyl consumption (µg)	Hypotension, nausea and vomiting, pruritus, shivering	Pre- eclampsia undergoing elective CS
Faiz 2013 [13]	Sensory block onset, sensory block duration	Shivering	Elective CS
Jabalameli 2012 [14]	-	Hypotension, nausea and vomiting, shivering, neurological deficit	Elective CS
Malleeswaran 2010 [15]	Time to T12, duration of spinal anesthesia, time to onset of motor block, time to complete motor block	Hypotension, nausea, pruritus	Pre- eclampsia undergoing elective CS
Paleti 2018 [16]	Onset of sensory blockade, onset of motor blockade, duration of sensory blockade, duration of motor blockade, time to first request of analgesia	Nausea, vomiting, shivering	Pre- eclampsia undergoing elective CS
Sachidananda 2018 [17]	-	Shivering, nausea, vomiting, bradycardia, hypotension, arrhythmia	Elective CS
Sun 2012 [18]	-	Shivering, bradycardia, hypotension, pruritus, nausea and vomiting	Elective CS
Unlugenc 2009 [19]	Onset of sensory block, duration of sensory block, onset of motor block, duration of motor block, duration of spinal anesthesia, time to first request of analgesic	Shivering, pruritus, nausea, vomiting, respiratory depression, hypotension, bradycardia	Elective CS
Xiao 2017 [20]	Sensory block onset time to T10, duration of sensory block, motor block onset time, duration of motor block, duration of anesthesia, consumption of fentanyl ( $\mu$ g)	Hypotension, nausea and vomiting, shivering, pruritus, severe sedation, re- spiratory depression, postdural puncture headache	Elective CS
Yousef 2010 [21]	Time to reach sensory block, time to reach maximum sensory block, recovery of motor block, onset of post operative pain, highest level of sensory block T4,T3,T2	Hypotension, nausea and vomiting, intra- operative pain or discomfort, post-opera- tive pain, shivering, pruritus, dizziness	Elective CS
Zhong 2018 [22]	Highest sensory level T4/T6, the onset of sensory block, the onset of motor block, duration of sensory block, duration of spinal anesthesia	Hypotension, pruritus, nausea and vomit- ing, shivering, uterine atonia	Pre- eclampsia undergoing elective CS

Table 1 has summarized all the endpoints which were reported in the original studies. The efficacy endpoints as well as the adverse drug events have been listed in the table. In addition, the type of cesarean section has also been listed (whether emergency or elective) Abbreviations CS: Cesarean section; T: Thoracic vertebra; µg: microgram

## Table 2 General features of the studies

Studies	Type of study	Enrollment time period	No of participants assigned to MgSO4 group (n)	No of partici- pants assigned to the control group (n)	
Elsharkawy 2018 [12]	Prospective randomized double blind study	-	30	30	
Faiz 2013 [13]	Randomized double blind controlled study	2011 - 2012	36	36	
Jabalameli 2012 [14]	Prospective doubled blind randomized trial	2010 - 2011	69	33	
Malleeswaran 2010 [15]	Randomized study	-	30	30	
Paleti 2018 [16]	Randomized clinical trial	2015	25	25	
Sachidananda 2018 [17]	Placebo controlled randomized double-blind pilot study	-	41	40	
Sun 2012 [18]	Prospective randomized double blind study	-	100	100	
Unlugenc 2009 [19]	Prospective, randomized, double blind study	-	30	30	
Xiao 2017 [20]	Prospective, double blinded, randomized, dose response trial	2014	30	30	
Yousef 2010 [21]	Prospective double blind randomized trial	-	45	45	
Zhong 2018 [22]	Randomized clinical trial	2015	30	30	
TOTAL no of participants (n)			466	429	

Table 2 lists the general properties of the original studies which have been included in this analysis. This includes the type of study, the year of participants' enrollment, and the number of participants in the experiment and the control group

Abbreviations MgSO4: Magnesium sulfate

Table 3         Baseline features of the participants									
Studies	Mean age (years)	BMI (kg/m <sup>2</sup> )	Gestational age (weeks)	SBP (mmHg)	DBP (mmHg)				
	Exp/Cntl	Exp/Cntl	Exp/Cntl	Exp/Cntl	Exp/Cntl				
Elsharkawy 2018 [12]	27.3/27.1	29.4/28.3	38.0/37.8	153.7/155.0	98.0/99.3				
Faiz 2013 [13]	26.2/27.2	27.6/27.9	-	-	-				
Jabalameli 2012 [14]	27.0/26.7	-	39.0/39.0	116.3/117.0	-				
Malleeswaran 2010 [15]	26.0/27.0	26.1/25.8	36.0/36.0	-	-				
Paleti 2018 [ <mark>16</mark> ]	23.0/26.0	27.9/28.8	-	-	-				
Sachidananda 2018 [17]	25.6/24.5	24.0/25.1	-	-	-				
Sun 2012 [18]	29.0/29.5	25.5/25.1	38.4/38.4	-	-				
Unlugenc 2009 [19]	-	29.3/29.1	36.9/37.3	-	-				
Xiao 2017 [ <mark>20</mark> ]	25.0/26.0	27.4/27.4	39.0/39.0	-	-				
Yousef 2010 [21]	34.5/35.0	28.7/25.6	-	-	-				
Zhong 2018 [22]	27.8/29.2	29.7/29.2	36.5/37.1	-	-				

Table 3 lists the baseline characteristics of the participants in the experimental as well as the control groups. Data concerning the mean age, the body mass index, the gestational age, the systolic blood pressure as well as the diastolic blood pressure have been listed

Abbreviations Exp: Experiment group; Cntl: Control group; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Kg/m<sup>2</sup>: Kilogram per meter square

was observed in sensory block onset (WMD: -0.54, 95% CI: -2.27 - 1.18; p = 0.54), motor block onset (WMD: 0.89, 95% CI: -0.50 - 2.27; p = 0.21) and time to first request of analgesia (WMD: 135.14, 95% CI: -23.42 - 293.70; p = 0.09) as shown in Fig. 4.

Consistent results were obtained throughout during sensitivity analysis. Publication bias was visually observed through funnel plot which was generated by the RevMan software and based on this visual assessment, there was little evidence of publication bias across all the studies that were involved in assessing the adverse drug events. The funnel plot has been illustrated in Fig. 5.

The results have been tabulated (Table 4).

### Discussion

In this analysis, we aimed to compare the adverse drug events observed with intrathecal MgSO4 as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section and our current results showed that intrathecal MgSO4 was associated with a significantly lower risk of shivering without causing any increase in other adverse drug events in patients undergoing elective CS. The risks of hypotension, bradycardia, pruritus, nausea and vomiting were not significantly increased with MgSO4. In addition, intrathecal MgSO4 was significantly effective when compared to a control group. It was associated with a significantly longer duration of sensory as well as motor blockade. The duration

Study or Subgroup         Events         Total         Vertical         Weight         M-H. Fixed. 455; Cl         M-H. Fixed. 455; Cl           Ehnstrany2016         0		MgSC	04	Contr	ol		Risk Ratio	Risk Ratio
1.1 A moving       6       0       1       0 <th0< th=""> <th< td=""><td>Study or Subgroup</td><td>Events</td><td>Total</td><td>Events</td><td>Total</td><td>Weight</td><td>M-H, Fixed, 95% C</td><td>I M-H, Fixed, 95% Cl</td></th<></th0<>	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
$ \begin{array}{c} \text{Each Constraints} \\ \text{Partice Constraints} \\ Partice Constr$	1.1.1 Shivering		20	47		0.00/	0 47 10 04 0 001	
$ \frac{1}{12} $	EISNARKAWY2018 Epiz2013	8	30	17	30	0.8%		
Pieter 2019 Sachdamard2019 S	Jabalameli2012	22	69	7	33	3.8%	1.50 [0.72, 3.16]	
Sachiadrand2018 16 41 2Z 40 10.9% 0.58 [0.37, 0.59] Unluger2009 13 1 100 4.4% 0.08 [0.01, 7.67] Sachiadrand2017 5 3 05 1 30 0.6% 0.38 [0.17, 7.67] Sachiadrand2018 1 30 1 4 30 0.6% 0.38 [0.17, 7.67] Sachiadrand2018 5 30 4 30 0.6% 0.30 [0.4% 10.0 [0.07, 15.26] Sachiadrand2018 2 2 4 20 (-0.10) [1.75] Sachiadrand2018 2 2 4 0.0 10.9% 0.57 [0.59] Helerogeneity: Ch = 13.84, 0f = 0 (-0.14), (F = 33% Treat for overall effect: Z = 1.32 ( $P = 0.001$ ) 1.12 Hypotensin Eshntrawy2018 8 30 4 30 16% 20 (0.67, 15.6] Sachiadrand2018 2 Z 41 17 40 0.6% 1.56 [0.68, 1.46] Sachiadrand2018 Z 4 31 (T 7 40 0.6% 1.56] (2.2, 2.6] Halerogeneity: Ch = 4.84, d = 0 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.05); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6% Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6%) Treat for overall effect: Z = 0.32 (P = 0.5); (P = 0.6%) Treat for overall effect: Z = 0.45 (P = 0.5); (P = 0.6%) Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6% Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6%) Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6% Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6% Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6%) Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6%) Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6%) Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6%) Treat for overall effect: Z = 1.32 (P = 0.23); (P = 0.6%) Treat for overall effect: Z = 1.32 (P =	Paleti2018	2	25	4	25	1.6%	0.50 [0.10, 2.49]	
Sun2012 1 100 11 100 4.4% 0.08 (0.01.0.69) Unlugare:2000 0 3 10 100 124% 0.83 (0.28, 2.44) Sub2017 5 30 6 30 2.4% 0.83 (0.28, 2.44) Sub2018 (95%, C1) 435 399 36.4% 0.63 (0.28, 2.44) Sub2018 (95%, C1) 436 399 36.4% 0.63 (0.48, 0.83) Labolar events 65 88 Heterogeneity: Ch = 13.8, df = 9 (P = 0.14); P = 33% Test for overall effect: Z = 3.24 (P = 0.14); P = 33% Test for overall effect: Z = 3.24 (P = 0.14); P = 33% Test for overall effect: Z = 3.24 (P = 0.14); P = 33% Test for overall effect: Z = 3.24 (P = 0.14); P = 0.55; P = 0.55; Heterogeneity: Ch = 6.8, df = 8 (P = 0.55; P = 0.5	Sachidananda2018	16	41	27	40	10.9%	0.58 [0.37, 0.90]	
Unbagenet2009 0 30 1 30 0 6% 0.33 (0.17, 767) Yound2010 3 45 9 440 3.6% 0.33 (0.10, 1.15) Subbala (95% C) 4.33 39 36.4% 0.083 (0.48, 0.83) Total events 65 88 Total events 75 10.00 17, 554 Test for overall effect: 2 = 3.22 ( $P = 0.001$ ) 1.1.2 Hypotension Total events 65 88 SurvD012 8 1 00 2 100 0 2% 100 (0.4, 6.86) Unbagenet2005 5 30 3 30 1.2% 157 (0.45, 1.96) Total events 65 96 82 2.357 5 1.10 (0.4, 6.86) Unbagenet2005 5 30 3 30 2.2% 157 (10.2, 2.86) Total events 65 96 96 2.33 1.1% 1.43 (0.31, 6.73) Malesevana.010 1 3 30 7 7 30 2.2% 157 (0.30, 1.90) Total events 65 96 98 2.33 1.1% 1.43 (0.31, 6.73) Malesevana.010 1 3 30 7 7 30 2.2% 158 (0.6, 4.00) Total events 65 96 98 2.33 1.1% 1.43 (0.31, 6.73) Malesevana.010 1 3 30 7 7 30 2.2% 158 (0.6, 4.00) Total events 65 48 30 3.2% 75 (0.30, 1.90) Total events 65 48 30 3.2% 75 (0.30, 1.90) Total events 75 0.30 2.0% 0.20 (0.02, 1.61) Malesevana.010 1 3 30 7 7 30 2.2% 158 (0.6, 4.00) Total events 75 0.47 ± 0.50, ( $P = 0.50$ ): 1.1.4 Purutus Test for overall effect: 2 = 0.35 ( $P = 0.50$ ): 1.1.4 Purutus Test for overall effect: 2 = 0.35 ( $P = 0.65$ ): 1.1.4 Purutus Test for overall effect: 2 = 0.35 ( $P = 0.65$ ): 1.1.4 Purutus Test for overall effect: 2 = 0.35 ( $P = 0.65$ ): 1.1.4 Purutus Test for overall effect: 2 = 1.37 ( $P = 0.25$ ); $P = 0.55$ ; 1.1.4 Purutus Test for overall effect: 2 = 0.32 ( $P = 0.65$ ): 1.1.4 Purutus Test for overall effect: 2 = 1.37 ( $P = 0.25$ ); $P = 0.55$ ; 1.1.4 Purutus Test for overall effect: 2 = 1.37 ( $P = 0.25$ ); $P = 0.55$ ; 1.1.4 Purutus Test for overall effect: 2 = 1.37 ( $P = 0.25$ ); $P = 0.55$ ; 1.1.4 Purutus Test for overall effect: 2 = 1.37 ( $P = 0.25$ ); $P = 0.55$ ; $P =$	Sun2012	1	100	11	100	4.4%	0.09 [0.01, 0.69]	
AdaCol 70 3 3 43 5 40 5 40 20 20 20 20 20 20 20 20 20 20 20 20 20	Unlugenc2009	0	30	1	30	0.6%	0.33 [0.01, 7.87]	
$ \begin{array}{c} \label{eq:point} \\ \mbox{log}(0,0) \\ \mb$	Xiao2017 Xeueef2010	5	30	6	30	2.4%	0.83 [0.28, 2.44]	
Subtracting (less: CD) $\frac{436}{10}$ $\frac{399}{36}$ $\frac{36}{40}$ , $0.63$ (0.44, 0.63) Heterogenetity: CD <sup>+</sup> = 1.34, df = 9 (P = 0.14); P = 33% Heterogenetic: Z = 3.22 (P = 0.001) <b>1.1.2 Hypotension</b> Elabarametricity: 2 31 60 15 73 36 21% Mathematicaticaticaticaticaticaticaticaticatic	Youset2010 Zhong2018	3	45	9	45	3.6%	1 00 [0 07 15 26]	
Total events 66 88 Heterogenety: CPi = 13.4; $\ell$ = 0.14; $\ell$ = 33% Test for vorall effect: Z = 3.22 (P = 0.001) 1.1.2 Hypotension Elshartawy2018 8 30 4 30 1.6% 2.00 (D.67, 5.94] Jabalame10012 33 69 15 33 8.1% 1.06 (D.67, 165] Starbitzli 20100 4 30 1 7 30 2.6% 0.57 (D.18, 175) Starbitzli 20100 12 100 2.2% 0.02 (D.18, 175) Starbitzli 20100 5 30 6 30 2.2% 0.75 (D.30, 190) Unlugent:2000 5 30 3 30 1.2% 0.75 (D.32, 190) Zhong2018 5 30 3 30 1.2% 0.76 (D.32, 2.08) Heterogenety: CPi = 0.83 (P = 0.55); $\ell$ = 0% Test for vorall effect: Z = 0.83 (P = 0.40) 1.13 Muses and Wornting Elsharkawy2018 1 00 5 00 2.0% Starbitzli (SC) 4 00 5 100 2.0% Starbitzli (SC) 4 00 9 100 3.6% 0.89 (D.21, 4.55) Starbitzli (SC) 4 00 9 100 3.6% 0.89 (D.21, 4.55) Starbitzli (SC) 4 00 9 100 3.6% 0.89 (D.33, 2.21) Unlugent:2000 4 100 9 100 3.6% 0.89 (D.33, 2.21) Unlugent:2000 4 100 9 100 3.6% 0.89 (D.33, 2.21) Unlugent:2000 1 3 00 7 30 2.8% 1.100 (D.22, 8.54) Unlugent:2000 1 3 00 1 2 30 1.0% 0.83 (D.33, 1.06) Starbitzli (SC) 2 22 6 0.05) 1.14 Purtus Elsharkawy2018 1 00 9 100 7.6% 0.83 (D.33, 1.06) Mallesewara010 1 2 00 12 0.05% 1.140 (D.27, 8.34) Unlugent:2000 1 30 0 2 30 1.0% 0.83 (D.33, 1.06) Mallesewara02010 1 2 0.05% 1.2% 0.07 (D.13, 2.00] Mallesewara02010 1 2 0.05% 1.2% 0.07 (D.13, 2.00] Mallesewara02010 1 2 0.0 2.8% 1.14 (H.72, 7.58) Mallesewara02010 1 2 0.0 2.8% 0.14 (H.72, 7.59) Multipercents 26 3.44 Heterogenety: CPI = 0.65); P = 0%; Test for vorall effect: Z = 1.24 (P = 0.25); P = 0%; Test for vorall effect: Z = 1.93 (P = 0.05); P = 729%; Test for vorall effect: Z = 1.93 (P = 0.05); P = 729; Total events 0 0 0 0 Not estimable Not estima	Subtotal (95% CI)		436		399	36.4%	0.63 [0.48, 0.83]	•
Heterogeneity: Ch <sup>2+</sup> = 13.4, df = 9 (P = 0.14); P = 33% Test for overall effect: Z = 3.22 (P = 0.001) 1.1.2 Hypotension Elsharkwy2018 a 3 0 4 30 1.6% 2.00 (0.67, 5.64] Jabalamel2012 33 69 15 33 5.1% 1.05 (0.67, 1.65] Malleeswaran2010 4 30 7 30 2.8% 0.57 (0.19, 1.75] SandD12 0 2 100 2 100 0.8% 1.58 (0.2, 2.36] SandD12 0 2 4 107 4 0 6.5% 1.58 (0.10, 2.36] SandD12 0 5 40 6 3 0 3, 2.4% 0.71 (0.24, 6.36] Subtol (95% Ct) 405 368 29.7% 1.11 [0.86, 1.44] Jobalamel2010 1 5 0 405 368 29.7% 1.11 [0.86, 1.44] Jobalamel2012 6 6 9 2 0 33; 1.1% 1.43 (0.31, 6.73] Malleeswaran2010 1 3 0 7 30 2.6% 0.20 (0.02, 1.61] Jabalamel2012 6 6 9 2 0 33; 1.5% 1.38 (0.58, 4.01] Test for overall effect: Z = 0.85 (P = 0.40): 1.13 Nausea and Vomiting Elsharkwy2018 3 30 2 30 0.8% 1.59 (0.24, 6.39] Heterogeneity: Ch <sup>2+</sup> = 6.8, df = 6 (P = 0.55); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.75); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.85); P = 0% Test for overall effect: Z = 0.45 (P = 0.25); P = 0% Test for o	Total events	65		88				
Test for varial effect: Z = 3.22 (P = 0.001) 1.1.2 Hypotension Elabarcawy2018 8 30 4 30 1.6% 2.00 (D.67, 5.94] Jabalameti2012 33 69 15 30 8.1% 1.05 (D.67, 1.65] Malesexwara010 4 30 14 7 40 6.9% 9.5% (D.27, 5.94] Unkagen:2000 5 30 6 30 2.4% 0.83 (D.28, 2.4) Valagen:2000 5 30 6 30 2.4% 0.83 (D.28, 2.4) Valagen:2000 5 4 30 8 30 2.2% 0.75 (D.30, 190) Total events 95 6 90 9 Heterogenety. Ch <sup>+</sup> = 6.8, d <sup>+</sup> = 6 (P = 0.55); P = 0% Test for vorsal effect: Z = 0.83 (P = 0.55); P = 0% Test for vorsal effect: Z = 0.83 (P = 0.40) 1.13 Nausea and Wormiting Elsharkawy2018 1 00 9 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 6 40 9 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 6 40 9 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 6 40 9 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 6 40 9 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 6 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 6 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 6 100 9 100 3.6% 0.89 (D.21, 4.55) Sun2012 8 100 9 100 7.6% 0.89 (D.21, 4.55) Sun2012 8 100 9 100 2.2% 0.57 (D.13, 30) Unkgenc2000 4 30 4 20 1.6% 0.30 (D.27, 6.34) Valagen2010 2 45 30 1.2% 0.77 (D.11, 3.90) Unkgenc2000 1 30 1 2 30 1.0% 0.20 (D.01, 4.00) Malesexwara010 1 2 30 1 9 30 7.6% 0.83 (D.38, 1.60) Sun2012 2 100 3 100 0.4% 0.20 (D.1, 4.00) Malesexwara0210 1 2 30 1 9 30 7.6% Test for voreal effect: Z = 1.24 (P = 0.25); P = 0% Test for voreal effect: Z = 1.29 (P = 0.59; P = 0% Test for voreal effect: Z = 1.39 (P = 0.24); P = 0% Test for voreal effect: Z = 1.39 (P = 0.24); P = 13% Test for voreal effect: Z = 1.39 (P = 0.24); P = 13% Test for voreal effect: Z = 1.39 (P = 0.24); P = 13% Test for voreal effect: Z = 1.39 (P = 0.24); P = 13% Test for voreal effect: Z = 1.39 (P = 0.24); P = 13% Test for voreal effect: Z = 1.47, <i>H</i> + 4.7, <i>H</i> + 0.4.005 (D = 0.24); P = 2.29 %	Heterogeneity: Chi <sup>2</sup> =	13.48, df =	= 9 (P =	0.14); l²	= 33%			
1.1.2 Hypotension         Elabatametic/21       3       6       3       1.6%       2.00 (0.7, 5.94)         Machimetic/21       3       6       17       40       2.5%       6.07 (1.45)         Machimetic/21       2       10       2       1.00 (0.14, 6.96)       1.00 (0.14, 6.96)         Sun2012       2       10       2       1.00 (0.14, 6.96)       1.00 (0.14, 6.96)         University       5       30       6       30       2.2%       7.6 (0.14, 6.36)         Youse/2010       5       4.5       7       4.5       1.00 (0.14, 6.36)       1.10 (0.24, 6.36)         Youse/2010       5       4.5       7       4.5       1.6% (1.02, 2.36)       1.11 (0.86, 1.44)         Total events       9.5       6.9       1.11 (0.86, 1.44)       1.11 (0.86, 1.44)       1.11 (0.86, 1.46)         Total events       2.5       1.5% (1.5% (0.14, 3.01)       1.11 (0.86, 1.46)       1.14 (0.81, 8.20)       1.14 (0.81, 8.20)         Saubtanet(0.27)       1       3.0       1.2% (0.86, 0.20) (0.21, 1.51)       1.11 (0.86, 1.46)       1.11 (0.86, 1.46)         University       1.3       0.0       1.30 (0.62, 8.63)       1.30 (0.62, 8.63)       1.30 (0.62, 8.63)       1.30 (0.62, 8.63)       1.30	Test for overall effect:	Z = 3.22 (	P = 0.00	1)				
1.12  proportions of the set	4.4.0 Illumeter airm							
Lability of the set o	T.1.2 Hypotension		20		20	1 69/	2 00 10 67 5 041	
	LISHARKAWY2010	33	- 50 69	4	30	1.0%	2.00 [0.67, 5.94]	<u> </u>
Sachidamanda2018 27 41 17 40 6.9% 1.05 [10.2, 2.96] Unitogene2009 5 30 6 30 2.4% 0.30 [0.14, 6.96] Vaca2017 6 30 8 30 2.4% 0.30 [0.2, 6.13] Vaca2017 6 30 8 30 2.4% 0.30 [0.2, 6.14] Vaca2010 5 45 7 45 2.8% 0.71 [0.24, 0.8] Subtal (95% C) 405 388 2.8.7% 1.11 [0.85, 1.4] Total events 95 69 Heterogeneity: Ch <sup>2</sup> = 6.8, df = 8 (P = 0.5); P = 0% Test for overal effect: Z = 0.33 (P = 0.40) 1.1.3 Nauses and Vomiting Elsharkawy2018 1 30 7 30 2.0% 0.20 [0.02, 1.61] Jubalame/2010 3 24 4.25 1.5% 0.75 [0.19, 3.01] Sachidamanda2018 3 41 3 40 1.2% 0.88 [0.36, 2.21] Unitogeneity: Ch <sup>2</sup> = 6.8, df = 9 (P = 0.76); P = 0% Test for overal effect: Z = 0.45 (P = 0.45); 1.1.4 Purutus Elsharkawy2018 1 30 1 30 0.4% 1.00 [0.27, 1.54] Unitogeneity: Ch <sup>2</sup> = 2.45 (P = 0.76); P = 0% Test for overal effect: Z = 0.45 (P = 0.76); P = 0% Test for overal effect: Z = 0.45 (P = 0.76); P = 0% Test for overal effect: Z = 0.45 (P = 0.76); P = 0% Test for overal effect: Z = 0.45 (P = 0.65); 1.1.4 Purutus Elsharkawy2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Unitogeneity: Ch <sup>2</sup> = 2.45 (f = 0.76); P = 0% Test for overal effect: Z = 0.45 (P = 0.65); 1.1.4 Purutus Elsharkawy2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Unitogeneity: Ch <sup>2</sup> = 2.45 (f = 0.65); P = 0% Test for overal effect: Z = 0.45 (P = 0.65); P = 0% Test for overal effect: Z = 0.45 (P = 0.65); P = 0% Test for overal effect: Z = 1.39 (P = 0.05); P = 0% Test for overal effect: Z = 1.39 (P = 0.05); P = 0% Test for overal effect: X = 1.39 (P = 0.05); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P = 0% Test for overal effect: X = 1.39 (P = 0.25); P =	Malleeswaran2010	4	30	7	30	2.8%	0.57 [0.19, 1.75]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Sachidananda2018	27	41	17	40	6.9%	1.55 [1.02, 2.36]	
Unliquenc2009 5 30 6 30 2.4% 0.83 (0.28, 2.44) Youse2010 5 45 7 45 2.8% 0.71 (0.24, 2.08) Subtal (95% C) 405 388 25.7% 1.11 [0.86, 1.4] Total events 95 60 Heterogeneity: Ch <sup>2</sup> = 6.83 (P = 0.40) 1.1.3 Nausea and Vontling Elsharkwy2018 1 30 7 30 2.0% 0.20 (0.02, 1.61) Jubalameli2018 3 25 4 2.5 1.6% 0.75 (0.19, 3.01) Paleit2018 3 25 4 2.5 1.6% 0.75 (0.19, 3.01) Sachidananda2018 3 41 3 40 1.2% 0.88 (0.21, 4.55) Sachidanand2018 3 41 3 40 1.2% 0.88 (0.21, 4.55) Sachidanand2018 3 41 3 40 1.2% 0.89 (0.32, 2.81) Unliquenc2009 4 30 4 30 1.6% 1.00 (0.28, 3.63) Youse2010 2 45 3 45 1.2% 0.67 (0.12, 3.80) Youse2010 3 0 2 30 0.8% 1.50 (0.27, 6.34) Subtal (95% C) 430 393 19.4% 1.08 (0.76, 1.54) Total events 55 48 Heterogeneity: Ch <sup>2</sup> = 5.80, df = 9 (P = 0.76), P = 0% Test for overal effect: Z = 0.45 (P = 0.65): 1.1.4 Pruntus Elsharkwy2018 0 30 2 30 1.0% 0.50 (0.27, 1.52) Xiao2017 2 3 100 3 100 1.2% 0.67 (0.11, 3.90) Unliquenc2009 1 30 1 30 0.4% 1.00 (0.07, 15.26) Xiao2017 2 4 100 3 100 0.4% 1.00 (0.07, 15.26) Xiao2017 2 3 100 1.30 0.4% 1.00 (0.07, 15.26) Xiao2017 2 3 100 1.00 0.4% 2.00 (0.19, 2.128) Xiao2017 2 2 100 1.00 0.4% 2.00 (0.19, 2.128) Xiao2017 2 3 0.00 0.0 30 Not estimable Subtatia (95% C) 295 295 13.7% 0.77 (0.51, 1.18, 05) Subtatia (95% C) 295 295 13.7% 0.77 (0.51, 1.80, 05) Subtatia (95% C) 295 295 13.7% 0.77 (0.51, 1.80, 05) Subtatia (95% C) 295 295 13.7% 0.77 (0.51, 1.80, 05) Subtatia (95% C) 177 1685 100.0% 0.51 (0.78, 1.06] Fist for overall effect: Z = 1.39 (P = 0.25): 1.1.5 Respiratory depression Unliquenc2009 0 30 0 30 Not estimable Not estim	Sun2012	2	100	2	100	0.8%	1.00 [0.14, 6.96]	
Xiao2017 6 30 8 30 3.2% 0.75 [0.30.190] Zhong2010 5 45 7 48 2.8% 0.71 [0.34, 0.63] Zhong2018 5 30 3 30 1.2% 1.71 [0.44, 0.63] Subtotal [95% C) 405 368 29.7% 1.11 [0.86, 1.46] Heterogeneity: Ch <sup>2</sup> = 0.83 ( $P = 0.40$ ) 1.1.3 Mausea and Voniting Elsharkawy2016 1 3 0 5 30 2.0% 0.20 [0.02, 1.61] Jabalameli2012 6 69 2 33 1.1% 1.43 [0.31, 6.73] Maleeswaran2010 13 30 7 30 2.8% 1.46 [0.86, 2.69] Paid(2018 3 25 4 25 1.6% 0.75 [0.19, 3.01] Sachidananda2018 3 41 3 40 1.2% 0.88 [0.21, 4.55] Subtotal [95% C] 2 43 3 4.13 40 1.2% 0.88 [0.21, 4.55] Voluere200 4 30 4 30 4.85% 0.89 [0.36, 2.21] Unlugenc2009 4 30 4 30 4.85% 1.00 [0.28, 3.21] Unlugenc2009 4 30 4 30 4.85% 1.00 [0.27, 8.34] Xiao2017 12 30 9 30 3.6% 1.30 [0.62, 2.89] Zhong2018 3 30 2 30 0.4% 1.00 [0.27, 8.34] Xiao2017 12 30 9 30 7.6% 0.40 [0.07, 8.34] Xiao2017 1 2 30 9 30 7.6% 0.40 [0.07, 8.34] Xiao2017 1 2 30 9 30 7.6% 0.40 [0.07, 8.34] Xiao2017 1 2 30 9 30 7.6% 0.20 [0.01, 4.00] Malierewarence: Ch <sup>2</sup> = 5.80, df = 9 (P = 0.76); P = 0% Test for overall effect: Z = 0.045 (P = 0.65) 1.1.4 Pruritue Elsharkawy2018 0 30 2 30 1.0% 0.20 [0.01, 4.00] Malierewarence: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.85); P = 0% Test for overall effect: Z = 1.24 (P = 0.22) 1.1.5 Bradycardia Sachidanand2018 5 41 0 40 0.2% 10.74 [0.61, 180.65] Subtotal (95% C) 295 295 13.7% 0.77 [0.51, 1.17] Total events 6 1 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.5); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 1.5% Total events 6 1 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 1.5% Total events 0 0 0 Heterogeneity: Ch <sup>2</sup> = 3.93 (P = 0.05); P = 1.2% Test for overall effect: Z = 1.93 (P = 0.05); P = 1.2% Test for overall effect: Z = 1.93 (P = 0.05); P = 1.2% Test for overall effect: Z = 1.93 (P	Unlugenc2009	5	30	6	30	2.4%	0.83 [0.28, 2.44]	
Yousef2010 5 45 7 45 28% 0.71 (0.24, 2.08) Subtal (95% C) 405 368 2.7% 1.11 (0.86, 1.44) Total events 95 69 Heterogeneity: Ch <sup>2</sup> = 6.83 ( $f^2 = 0.5$ ); $f^2 = 0.5$ Test for overall effect: $Z = 0.83 (P = 0.5$ ); $f^2 = 0.5$ Li.1 (0.86, 4.00) Heterogeneity: Ch <sup>2</sup> = 6.84 ( $f^2 = 0.5$ ); $f^2 = 0.5$ Sachidananda2018 3 41 3 0.0 2.0% 0.20 (0.02, 1.61) Jubalamei2010 6 69 2 33 1.1% 1.48 (0.86, 4.00) Paleti2018 3 225 4 225 1.6% 0.75 (0.19, 3.01) Malleeswaran.2010 13 30 7 30 2.8% 1.86 (0.86, 4.00) Paleti2018 3 225 4 25 1.6% 0.75 (0.19, 3.01) Maleeswaran.2010 12 45 0.09 9 100 3.6% 0.89 (0.36, 2.21) Uniugenc2009 4 30 4 30 1.6% 1.00 (0.28, 3.63) Subctal (95% C) 430 30 2 30 1.0% 0.20 (0.01, 4.00) Maleeswaran.2011 22 45 0.80; $f^2 = 0.75$ ; $f^2 = 0.5$ L1.4 Pruritus Elsharkawy2018 0 30 2 30 1.0% 0.20 (0.01, 4.00) Maleeswaran.2010 12 30 19 30 7.6% 0.63 (0.31, 3.10) Subctal (95% C) 245 1 48 0.4% 2.00 (0.19, 2.12, 3.00) Subctal (95% C) 245 1 45 0.4% 0.4% 0.00 (0.7, 15.26) Julagenc2009 1 30 1 30 0.4% 1.00 (0.7, 15.26) Xiao2017 2 100 3 10 1.2% 0.67 (0.11, 3.00) Uniugenc2009 1 30 1 30 0.4% 1.00 (0.7, 15.26) Xiao2017 2 100 3 10 0.02% 10.74 (0.61, 188.05) Subtatal (95% C) 25 295 13.7% 0.77 (0.51, 10.6) Subtatal (95% C) 25 295 13.7% 0.77 (0.51, 1.68, 05) Subtatal (95% C) 171 170 0.8% 4.45 (0.97, 20.38) Subtatal (95% C) 217 1 0.00 0.2% 10.74 (0.61, 188.05) Subtatal (95% C) 171 170 0.8% 4.45 (0.97, 20.38) Subtatal (95% C) 217 1 0.00 0.2% 10.74 (0.61, 188.05) Subtatal (95% C) 171 170 0.8% 4.45 (0.97, 20.38) Subtatal (95% C) 1777 1685 10.0.0% 0.91 (0.78, 1.66) Subtatal (95% C) 1777 1685 10.0.0% 0.91 (0.78, 1.66) Favours (Mg8Od4) Favours (control) Favours (Mg8Od4) Favours (control)	Xiao2017	6	30	8	30	3.2%	0.75 [0.30, 1.90]	
Zhong2018 5 30 3 30 12% [1,27] (4,4,6,36] Total events 95 69 Heterogeneity: Ch <sup>2</sup> = 0.83 (P = 0.40) <b>1.1.3 Nausea and Voniting</b> Elsharkawy2016 1 30 5 30 2.0% 0.20 [0.02, 1.61] Jabalameli2012 6 69 2 33 1.1% 1.43 [0.31, 6.73] Maleeswaran2010 13 30 7 30 2.8% 1.46 [0.86, 0.04] Pakt2018 3 2.5 4 2.5 1.6% 0.75 [0.19, 3.01] Sachidananda2018 3 41 3 40 1.2% 0.98 [0.21, 4.53] Sachidananda2018 3 41 3 40 1.2% 0.98 [0.21, 4.53] Zhong2018 3 30 2 30 0.8% 1.50 [0.27, 8.34] Subtotal (95% CI) 430 3 393 19.4% 1.08 [0.76, 1.54] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 5.40, d <sup>2</sup> = 9 (P = 0.76); P = 0% Test for overall effect: Z = 0.45 (P = 0.65): <b>1.1.4 Puritus</b> Elsharkawy2016 0 30 2 30 1.0% 0.20 [0.01, 4.00] Maleeswaran2010 12 30 19 30 7.6% 0.63 [0.38], 1.68] Subtotal (95% CI) 295 295 13.7% 0.77 [0.51, 1.17] Yousef2010 2 445 1 445 0.4% 2.00 [0.13, 7.83] Subtotal (95% CI) 295 295 13.7% 0.77 [0.51, 1.17] Yousef2010 2 445 1 450 0.4% 2.00 [0.13, 2.18] Yousef2010 2 2 40 01 1 00 0.4% 2.00 [0.13, 2.18] Yousef2010 2 2 45 1 450 0.4% 2.00 [0.13, 2.18] Yousef2010 2 2 45 1 450 0.4% 2.00 [0.13, 2.18] Yousef2010 2 2 45 1 450 0.4% 2.00 [0.13, 2.18] Yousef2010 2 445 1 450 0.4% 2.00 [0.13, 2.18] Yousef2010 2 2 100 1 100 0.4% 2.00 [0.13, 2.18] Yousef2010 2 2 100 1 100 0.4% 2.00 [0.13, 2.18] Subtotal (95% CI) 171 0 30 0.2% 4.074 [0.51, 180.05] Subtotal (95% CI) 171 0 130 0.4% 4.45 [0.57, 2.3.6] Heterogeneity: Ch <sup>2</sup> = 0.65; P = 0.05; <b>1.1.5 Fradycardia</b> Sachidananda2018 5 41 0 40 0 25% (0.74 [0.51, 180.05] Subtotal (95% CI) 177 1 685 100.0% 0.91 [0.13, 7.08] Heterogeneity: Ch <sup>2</sup> = 0.66; P = 0.65; P = 0.5% Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 0.66; P = 0.65; P = 0.5% Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 4.3.9; (f = 3.8] (P = 0.2%); P = 1.5% Total events 26 40 60 Not estimable Not estimable Not estimable Not estimable Not estimable Yousef204 Favours [contro]	Yousef2010	5	45	7	45	2.8%	0.71 [0.24, 2.08]	
Subtool (95% CI) 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2	Zhong2018 Subtotal (05% CI)	5	30	3	30	1.2%	1.67 [0.44, 6.36]	<b>.</b>
Luis events $24$ ( $146$ ( $146$ ) ( $146$ ( $14$	Subtotal (95% CI)	05	405	60	308	29.7%	1.11 [0.86, 1.44]	T
The star for overall effect $Z = 0.30$ (ff = 0.40) 1.1.3 Nausea and Vomiting Elsharkawy2018 1 30 5 30 2.0% 0.20 (0.02, 1.61) Jabatameli2012 6 6 69 2 33 1.1% 1.43 (0.21, 6.73) Malleswaran.2010 13 30 7 30 2.8% 1.86 (0.06, 4.00) Pateti2018 3 225 4 25 1.6% 0.98 (0.36, 2.21) Uniugenc2009 4 30 4 30 1.6% 1.00 (0.28, 3.63) Xiao2017 12 30 9 30 3.6% 1.00 (0.27, 6.1.54) Total events 55 48 Heterogeneity: Ch <sup>2</sup> = 5.80, df = g (P = 0.76); P = 0% Test for overall effect: Z = 0.45 (P = 0.65) 1.1.4 Puritus Elsharkawy2018 0 30 2 30 1.0% 0.20 (0.01, 4.00) Uniugenc2009 1 30 1 30 0.4% 1.00 (0.07, 15.26) Uniugenc2009 1 20 1 30 0.4% 1.00 (0.01, 5.26) Sur2012 2 100 3 100 1.2% 0.67 (0.11, 3.90) Uniugenc2009 1 30 1 30 0.4% 1.00 (0.01, 5.26) Sur2012 2 45 1 4.5 0.4% 2.00 (0.19, 21.38) Zhong2018 0 30 2 295 13.7% 0.77 (0.51, 1.17) Youse(2010 2 445 1 4.5 0.4% 2.00 (0.19, 21.38) Subtotal (9% CI) 284 5 1 0 40 0.2% 10.74 (0.61, 188.05) Sur2012 2 100 1 100 0.4% 3.00 (0.13, 70.83) Subtotal (9% CI) 283 295 13.7% 0.77 (0.51, 1.17) Total events 8 1 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.35); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 1.07% Test for overall effect: Z = 1.93 (P = 0.05); P = 72.9%	Heterogeneity: Chi <sup>2</sup> = I	95 688 df=1	8 (P = 0	55)· I <sup>2</sup> =	0%			
1.1.3 Nausea and Vomiting         Eisharkawy2018       1       30       5       30       2.0%       0.20 [0.02, 1.61]         Jabalameil2012       6       69       2       33       1.1%       0.40 [0.16, 73]         Maleswara2010       13       30       7       30       2.8%       1.86 [0.66, 4.00]         Patet2016       3       2.5       4       2.5       1.6%       0.75 [0.19, 3.01]         Sachidananda2018       3       41       3       40       1.2%       0.89 [0.21, 4.55]         Unlugenc2009       4       30       1.6%       0.09 [0.36, 2.21]       Unlugenc2016       2.30       0.67 [0.12, 3.80]         Zhong2018       3       30       2.30       0.8%       1.50 [0.27, 8.34]       Subtotal (6% Cf)       439       393       1.9.4%       1.08 [0.76, 1.54]         Heterogeneity: Chi" = 5.80, df = 0 = 0.76;       1       30       1.30       0.4%       1.00 [0.07, 15.26]       Subtotal (6% Cf)       2.30       1.30       0.4%       1.00 [0.07, 15.26]       Subtotal (6% Cf)       2.295       3.27%       0.74 [0.61, 188.05]       Subtotal (6% Cf)       1.30       0.30       0.2%       3.00 [0.3, 7.20.36]       Image: 1.30 [0.1, 7.72, 2.6]       Image: 1.37%       0.7	Test for overall effect:	Z = 0.83 (	P = 0.40	.55), 1 - )	0 /0			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		(		,				
Elsharkawy2018 1 30 5 30 2.0% 0.20 [0.02, 1.61] Mallesewaran2010 13 30 7 30 2.8% 1.86 [0.86, 4.00] Paleti2018 3 25 4 25 1.6% 0.75 [0.19, 3.01] Sachidananda2018 3 41 3 40 1.2% 0.38 [0.21, 4.55] Sun2012 8 100 9 100 3.6% 0.38 [0.36, 2.21] Unlugenc2009 4 30 4 30 1.6% 0.05 [0.19, 3.06] Xias2017 12 30 9 30 2.30 0.8% 1.50 [0.27, 8.34] Zhong2018 3 30 2 30 0.8% 1.05 [0.27, 8.34] Vousef2010 2 45 3 45 1.2% 0.67 [0.12, 3.60] Zhong2018 3 30 2 30 0.8% 1.05 [0.27, 8.34] Heterogeneity. Ch <sup>2</sup> = 5.80, df = 9 ( $P = 0.76$ ); $P = 0\%$ Test for overall effect: Z = 0.45 ( $P = 0.65$ ) 1.1.4 Pruritus Elsharkawy2018 0 30 2 30 1.6% 0.20 [0.01, 4.00] Mallesswaran2010 12 30 19 30 7.6% 0.20 [0.01, 4.00] Mallesswaran2010 12 30 19 30 7.6% 0.20 [0.01, 4.00] Mallesswaran2010 12 30 19 30 7.6% 0.20 [0.01, 4.27] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Zhong2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Xiac2017 2 45 1 45 0.4% 2.00 [0.19, 21.28] Zhong2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Xiac2017 2 45 14 0 0.40 0.2% 10.74 [0.61, 188.05] Subtotal (95% Cl) 295 245 13.7% 0.77 [0.51, 1.17] Total events 8 1 1 Heterogeneity. Ch <sup>2</sup> = 2.8, df = 6 ( $P = 0.85$ ); $P = 0\%$ Test for overall effect: Z = 1.32 ( $P = 0.05$ ); $P = 0\%$ Test for overall effect: Z = 1.33 ( $P = 0.05$ ); $P = 0\%$ Test for overall effect: Z = 1.33 ( $P = 0.05$ ); $P = 0\%$ Test for overall effect: Z = 1.33 ( $P = 0.24$ ); $P = 13\%$ Total (95% Cl) 177 1885 100.0% 0.91 [0.78, 1.06] Xiao2017 0 30 0 30 Not estimable Xiao2017 17 0 30 0 30 Not estimable Xiao2017 0 30 0 0 30 Not estimable Xiao2017 0 30 0 30 Not estimable Xiao2017 0 30 0 30 Not estimable Xiao2017 0 1797 1685 100.0% 0.91 [0.78, 1.06] Total (95% Cl) 1797 1685 100.0% 0.91 [0.78, 1.06] Total (95% Cl) 1979 198 ( $P = 0.24$ ); $P = 13\%$ Test for overall effect: X = 1.19 ( $P = 0.23$ ) Test for overall effect: K = 1.47, Clf = 4 ( $P = 0.05$ ); $P = 72.9\%$	1.1.3 Nausea and Vor	miting						
Jabalameli2012 6 6 69 2 33 1.1% 1.38 [0.36, 4.00] Palet2018 3 25 4 25 1.6% 0.75 [0.19, 3.01] Sachidananda218 3 41 3 04 1.2% 0.88 [0.38, 2.21] Unlugenc2009 4 30 4 30 1.6% 0.98 [0.38, 2.21] Unlugenc2009 4 30 4 30 1.6% 1.00 [0.28, 3.63] Sub2017 1 2 30 9 30 3.6% 1.33 [0.66, 2.69] Yousel2010 2 45 3 45 1.2% 0.67 [0.12, 3.80] Sub2012 3 3 30 2 30 0.8% 1.50 [0.27, 8.34] Subtotal (95% C1) 430 33 19.4% 1.08 [0.76, 1.54] Heterogeneity: Ch <sup>2</sup> = 5.80, df = 9 (P = 0.76); P = 0% Test for overall effect: Z = 0.45 (P = 0.65) 1.1.4 Provintus Elsharkawy2018 0 30 2 30 1.0% 0.20 [0.01, 4.00] Malleswaran2010 12 30 19 30 7.6% 0.63 [0.38, 1.06] Sub2012 2 100 3 100 1.2% 0.67 [0.11, 3.90] Unlugenc2009 1 30 1 30 0.4% 1.00 [0.07, 15.26] Sub2011 2 4 55 1 4.55 0.48 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.83); P = 0% Test for overall effect: Z = 1.24 (P = 0.25) 1.1.5 Bradycardla Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Sub2012 2 100 1 100 0.4% 2.00 [0.18, 2.171] Ordal events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.85); P = 0% Test for overall effect: Z = 1.24 (P = 0.65); P = 0% Test for overall effect: Z = 1.24 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.05) 1.1.6 Respiratory depreesion Unlugenc2009 0 30 0 30 Not estimable Xiab2017 0 30 0 30 Not estimable Test for overall effect: Z = 1.19 (P = 0.23); Test for subrout difference: C = 1.43 (H = 2.02); P = 13% Total events 0 0 0 Heterogeneity: Ch <sup>2</sup> = 4.331, H = 38 (P = 0.02); P = 13% Test for overall effect: Z = 1.19 (P = 0.23); Test for overall effect: Z = 1.19 (P = 0.23); Test for overall effect: Z = 1.19 (P = 0.23); Test for overall effect: Z = 1.19 (P = 0.23); Test for overall effect: C = 1 = 4.4 (P = 0.05); P = 72.9%	Elsharkawy2018	1	30	5	30	2.0%	0.20 [0.02, 1.61]	
Malleeswaran2010 13 30 7 30 2.8% 1.88 (0.86, 4.00) Sachidananda2018 3 41 3 40 12% 0.76 (1.91 3.01] Sachidananda2018 3 41 3 40 12% 0.76 (1.91 3.01] Unlugenc2000 4 30 4 30 1.6% 0.89 (0.36, 2.21] Unlugenc2000 4 30 4 30 1.6% 1.00 (0.28, 3.63] Subtotal (95% CI) 2 45 3 45 1.2% 0.67 (0.12, 3.60] Total events 55 48 Heterogeneity: Ch <sup>2</sup> = 5.80, df = 9 (P = 0.76); $\mu = 0\%$ Test for overall effect: $Z = 0.45$ (P = 0.65) 1.1.4 Pruritus Elsharkawy2018 0 30 2 30 1.0% 0.20 (0.01, 4.00] Malleeswaran2010 12 30 19 30 7.6% 0.63 (0.38, 1.66] Sun2012 2 100 3 100 1.2% 0.67 (0.11, 3.90] Unlugenc2009 1 30 1 30 0.4% 1.00 (0.07, 15.26] Subtotal (95% CI) 2 45 1 45 0.4% 2.00 (0.19, 21.28] Zhong2018 1 30 1 30 0.4% 1.00 (0.07, 15.26] Subtotal (95% CI) 2 25 225 13.7% 0.77 (0.51, 1.17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.85); $\mu = 0\%$ Test for overall effect: $Z = 1.32 (P = 0.65); \mu = 0\%$ Test for overall effect: $Z = 1.32 (P = 0.65); \mu = 0\%$ Total events 8 1 1 Total events 8 1 1 Total events 8 1 1 Total events 0 0 0 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); $\mu = 0\%$ Test for overall effect: $Z = 1.33 (P = 0.05)$ 1.1.6 Respiratory depression Unlugenc2009 0 30 0 30 Not estimable Nate stimable Total events 0 0 0 Heterogeneity: Ch <sup>2</sup> = 4.334, df = 38 (P = 0.24); $\mu = 13\%$ Total events 24 24 240 Heterogeneity: Ch <sup>2</sup> = 4.34, df = 38 (P = 0.24); $\mu = 13\%$ Total events 24 24 240 Heterogeneity: Ch <sup>2</sup> = 4.34, df = 38 (P = 0.24); $\mu = 13\%$ Total events 0 0 0 Heterogeneity: Ch <sup>2</sup> = 4.34, df = 38 (P = 0.24); $\mu = 13\%$ Total events 24 24 240 Heterogeneity: Ch <sup>2</sup> = 4.34, df = 38 (P = 0.24); $\mu = 13\%$ Test for subroad effect: $Z = 1.19 (P = 0.23)$ Test for overall effect: $Z = 1.19 (P = 0.23)$ Test for overall effect: $Z = 1.19 (P = 0.23)$ Test for overall effect: $Z = 1.19 (P = 0.23)$ Test for overall effect: $Z = 1.19 (P = 0.23)$ Test for overall effect: $Z = 1.19 (P = 0.23)$ Test for overall effect: $Z = 1.19 (P = 0.23)$ Test for subroad differences: $Ch^2 = 1.47 \cdot df = 4 (P $	Jabalameli2012	6	69	2	33	1.1%	1.43 [0.31, 6.73]	
Particulus 3 2 4 2 3 1.5% 0.79 [0.19, 3.01] Sachidamada2018 3 41 3 40 1.2% 0.38 [0.28, 3.63] Subota 1(95% C) 430 4 30 1.6% 0.38% 0.28 [0.36, 2.21] Unlugen22009 4 30 4 30 1.6% 1.00 [0.28, 3.63] Viouse[2010 2 45 3 45 1.2% 0.67 [0.12, 3.80] Subota 1(95% C) 430 393 19.4% 1.08 [0.76, 1.54] Total events 55 48 Heterogeneity: Ch <sup>2</sup> = 5.80, df = 9 (P = 0.76); P = 0% Test for overall effect: 2 = 0.45 (P = 0.65): 1.1.4 Pruritus Elsharkawy2018 0 30 2 30 1.0% 0.20 [0.01, 4.00] Unlugen22009 1 30 1 30 0.4% 1.00 [0.07, 15.26] Subota 1(95% C) 2 95 2 295 13.7% 0.77 [0.51, 1.17] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Subota 1(95% C) 2 95 2 295 13.7% 0.77 [0.51, 1.17] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Subota 1(95% C) 2 95 2 295 13.7% 0.77 [0.51, 1.17] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Subota 1(95% C) 2 95 2 295 13.7% 0.77 [0.51, 1.17] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Subota 1(95% C) 2 95 2 295 13.7% 0.77 [0.51, 1.17] Total events 2 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.33); P = 0% Test for overall effect: 2 = 1.24 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.65); P = 0% Test for overall effect: 2 = 1.93 (P = 0.65); P = 0% Test for overall effect: 2 = 1.93 (P = 0.65); P = 0% Test for overall effect: 2 = 1.93 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.05); P = 0% Test for overall effect: 2 = 1.93 (P = 0.24); P = 13% Heterogeneity: Ch <sup>2</sup> = 3.91, df = 38 (P = 0.24); P = 13% Heterogeneity: Ch <sup>2</sup> = 3.91, df = 38 (P = 0.24); P = 13% Total events 0 0 0 Heterogeneity: Ch <sup>2</sup> = 4.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23); P = 0.05); P = 72.9%	Malleeswaran2010	13	30	7	30	2.8%	1.86 [0.86, 4.00]	
Sach Mahambazoris 3 4,1 3 4,0 1,2,8 0,30 ( $p$ ,2,1,4,3,5) Unlugenc2009 4 30 4 30 1,6% 1,00 ( $p$ ,28, 3,63] Vousef2010 2 45 3 45 1,2% 0,67 ( $p$ ,12, 3,80] Vousef2010 2 45 3 45 1,2% 0,67 ( $p$ ,12, 3,80] Subtotal (95% C) 430 393 19,4% 1,08 ( $p$ ,76, 1,54] Total events 55 48 Heterogeneity: Ch <sup>2</sup> = 5,80, df = 9 ( $P$ = 0,76); $P$ = 0% Test for overall effect: Z = 0,45 ( $P$ = 0,65) 1.1 <i>A</i> Puritus Elsharkawy2018 0 30 2 30 1,0% 0,30 ( $p$ ,30, 3, 1,06] Sun2012 2 100 3 100 1,2% 0,63 ( $p$ ,38, 1,60] Sun2012 2 100 3 100 1,2% 0,67 ( $p$ ,11,3,90] Unlugenc2009 1 30 1 30 0,4% 1,00 ( $p$ ,07, 15,26] Xiao2017 8 30 7 30 2,4% 1,14 ( $p$ ,47, 2,75] Vousef2010 2 45 1 45 0,4% 2,00 ( $p$ ,19, 21,28] Zhong2018 1 30 1 30 0,4% 1,00 ( $p$ ,07, 15,26] Xiao2017 8 30 7 30 2,2% 1,14 ( $p$ ,47, 2,75] Vousef2010 2 45 1 45 0,4% 2,00 ( $p$ ,19, 21,28] Zhong2018 1 30 1 30 0,4% 1,00 ( $p$ ,07, 15,26] Xiao2017 8 30 7 30 0,2% 3,00 ( $p$ ,13, 70 8,3] Subtotal (95% C) 2195 295 13,7% 0,77 ( $p$ ,51, 1,17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 0,48, df = 2 ( $P$ = 0,63); $P$ = 0% Test for overall effect: Z = 1,24 ( $P$ = 0,25); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,05); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,05); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,25); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,05); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,25); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,25); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,25); $P$ = 0% Test for overall effect: Z = 1,28 ( $P$ = 0,25); $P$ = 0% Test for overall effect: Z = 1,39 ( $P$ = 0,25); $P$ = 0% Test for overall effect: Z = 1,39 ( $P$ = 0,24); $P$ = 13% Total events $Q$ = 240 Heterogeneity: Ch <sup>2</sup> = 43,91, df = 38 ( $P$ = 0,24); $P$ = 13% Test for overall effect: Z = 1,19 ( $P$ = 0,23) Test for overall effect: Z = 1,19 ( $P$ = 0,24); $P$ = 13% Test for overall effect: Z = 1,19 ( $P$ = 0,24); $P$ = 13% Test for overall effect: Z = 1,19 ( $P$ = 0,24); $P$ = 13% Total (eyents $Q^2$ = 240 Heterogeneity	Paleti2018 Sachidapando2018	3	25	4	25	1.6%	0.75 [0.19, 3.01]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Sachidanandazo io Sun2012	3	100	9	100	3.6%	0.98 [0.21, 4.33]	
Xiao2017       12       30       9       30       3.6%       1.33       [0.66, 2.69]         Yousef2010       2       45       3       45       1.2%       0.67       [0.72, 8.34]         Subtotal (95% CI)       430       393       19.4%       1.08       [0.76, 1.54]         Total events       55       48         Heterogeneity: Chi" = 5.80, df = 9 (P = 0.76); P = 0%       Test for overall effect: Z = 0.45 (P = 0.65)         1.1.4 Pruritus       Elsharkawy2018       0       30       7.6%       0.63 (0.38, 1.06)         Subtotal (95% CI)       10       100       1.2%       0.67 (0.11, 3.90)       0         Uniugene2009       1       30       1.30       0.4%       1.00 (0.07, 15.26)       1.45         Yousef2010       2       45       1.45       0.4%       2.00 (0.19, 21.28)       1.46         Zhong2018       1       30       0.4%       1.00 (0.07, 15.26)       1.47       1.7%         Subtotal (95% CI)       2       10       40       0.2%       10.77 (0.51, 1.17)       1.48         Vousef2010       2       10       0.04%       2.00 (0.18, 21.71)       1.48       1.49         Subtotal (95% CI)       171       10 </td <td>Unlugenc2009</td> <td>4</td> <td>30</td> <td>4</td> <td>30</td> <td>1.6%</td> <td>1.00 [0.28, 3.63]</td> <td></td>	Unlugenc2009	4	30	4	30	1.6%	1.00 [0.28, 3.63]	
YouseR2010       2       4       5       3       45       1.2%       0.67       [0.12, 3.80]         Zhong2018       3       30       2       30       0.8%       1.50       [0.27, 8.34]         Subtotal (95% CI)       430       393       1.4%       1.08       [0.76, 1.54]         Heterogeneity: Ch <sup>2</sup> = 5.0.45 (P = 0.65)       1.4%       0.83       [0.76, 1.54]         1.4 Pruritus       Elsharkawy2018       0       30       2       30       1.0%       0.20 [0.01, 4.00]         Sun2012       2       100       3       100       1.2%       0.67 [0.11, 3.90]         Unlugenc2009       1       30       1       30       0.4%       1.00 [0.07, 15.26]         Zhong2018       1       30       1       30       0.4%       1.00 [0.07, 15.26]         Subtotal (95% CI)       295       295       13.7%       0.77 [0.51, 1.17]         Total events       26       34         Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.83); P = 0%         Test for overall effect: Z = 1.93 (P = 0.05)         1.1.5 Bradycardia       5         Sachidamand2018       5       41       0.40       0.2%       10.01, 3.70.83]       10.130       0.8	Xiao2017	12	30	9	30	3.6%	1.33 [0.66, 2.69]	- <del> </del>
$ \frac{2 \log_2 218}{\text{Subtotal (95\% CI)}} 3 3 0 2 3 0 0.8\% 1.50 [0.27, 8.34] \\ \frac{3 33}{\text{Subtotal (95\% CI)}} 430 333 19.4\% 1.08 [0.76, 1.54] \\ 1.08 [0.76, 1.54] \\ 1.08 [0.76, 1.54] \\ 1.4 \text{ Puritus} \\ Elsharkay/2018 0 30 2 30 1.0\% 0.20 [0.01, 4.00] \\ Malleeswaran2010 12 30 19 30 7.6\% 0.63 [0.38, 1.06] \\ Sun2012 2 100 3 100 1.2\% 0.67 [0.11, 3.90] \\ Unlugenc2009 1 30 1 30 0.4\% 1.00 [0.07, 15.26] \\ Xiao2017 8 30 7 30 2.8\% 1.14 [0.47, 2.75] \\ Yousef2010 2 45 1 45 0.4\% 2.00 [0.07, 15.26] \\ Subtotal (95\% CI) 295 295 13.7\% 0.77 [0.51, 1.17] \\ Total events 26 34 \\ Heterogeneity: Ch2 = 2.44, df = 6 (P = 0.83); P = 0\% \\ Test for overall effect: Z = 1.24 (P = 0.22) \\ 1.1.5 Bradycardia \\ Sachidananda2018 5 41 0 40 0.2\% 10.74 [0.61, 188.05] \\ Subtotal (95\% CI) 1717 170 0.8\% 4.45 [0.97, 20.36] \\ Total events 8 1 \\ Heterogeneity: Ch2 = 0.86, df = 2 (P = 0.65); P = 0\% \\ Test for overall effect: Z = 1.93 (P = 0.05) \\ 1.1.6 Respiratory depression \\ Unlugenc2009 0 30 0 30 0 X0 tot estimable \\ Subtotal (95\% CI) 1777 1685 100.0\% 0.91 [0.78, 1.06] \\ Subtotal (95\% CI) 60 60 \\ Not estimable \\ Subtotal (95\% CI) 1777 1685 100.0\% 0.91 [0.78, 1.06] \\ Heterogeneity: Ch2 = 4.391, df = 38 (P = 0.24); P = 13\% \\ Test for overall effect: Z = 1.9 (P = 0.22) \\ 1.16 Respiratory depression \\ Unlugenc2009 0 30 0 30 0 Not estimable \\ Subtotal (95\% CI) 1777 1685 100.0\% 0.91 [0.78, 1.06] \\ Heterogeneity: Ch2 = 4.391, df = 38 (P = 0.24); P = 13\% \\ Test for overall effect: Z = 1.19 (P = 0.23) \\ Test for overall effect: C = 1.19 (P = 0.23) \\ Test for overall effect: Ch2 = 1.77, df = 4 (P = 0.05); P = 72.9\% \\ \end{bmatrix}$	Yousef2010	2	45	3	45	1.2%	0.67 [0.12, 3.80]	
Subtotal (95% CI) 430 393 19.4% 1.08 [0.76, 1.54] Total events 55 48 Heterogeneity: Ch <sup>2</sup> = 5.80, df = 9 (P = 0.76); P = 0% Test for overall effect: Z = 0.45 (P = 0.65) 11.4 Pruritus Elsharkawy2018 0 30 2 30 1.0% 0.20 [0.01, 4.00] Malleeswaran2010 12 30 19 30 7.6% 0.63 [0.38, 1.06] Sun2012 2 100 3 100 1.2% 0.67 [0.11, 3.90] Unlugenc2009 1 30 1 30 0.4% 1.00 [0.07, 15.26] Subtotal (95% CI) 295 295 13.7% 0.77 [0.51, 1.17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.33); P = 0% Test for overall effect: Z = 1.24 (P = 0.22) 1.1.5 Bradycardia Sachidannad2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Subtotal (95% CI) 171 170 0.8% 4.45 [0.97, 20.36] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.05) 1.1.6 Respiratory depression Unlugenc2009 0 30 0 30 Not estimable Subtotal (95% CI) 171 170 0.8% 4.45 [0.97, 20.36] Total events 0 0 0 Heterogeneity: Ch <sup>2</sup> = 43.91, df = 38 (P = 0.24); P = 13% Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 43.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23); P = 13% Test for overall effect: Z = 1.19 (P = 0.23); P = 12.9%	Zhong2018	3	30	2	30	0.8%	1.50 [0.27, 8.34]	
Total events 55 48 Heterogeneity: Ch <sup>2</sup> = 5.0 (df = 9 (P = 0.76); P = 0% Test for overall effect: Z = 0.45 (P = 0.65) 1.1.4 Pruritus Elsharkawy2018 0 30 2 30 1.0% 0.20 [0.01, 4.00] Malleeswaran2010 12 30 19 30 7.6% 0.63 [0.38, 1.06] Sun2012 2 100 3 100 1.2% 0.67 [0.11, 3.90] Unlugenc2009 1 30 1 30 0.4% 1.00 [0.07, 15.26] Xiao2017 8 30 7 30 2.8% 1.14 [0.47, 2.75] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Zhong2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Subtotal (95% Cl) 295 295 13.7% 0.77 [0.51, 1.17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84 df = 6 (P = 0.83); P = 0% Test for overall effect: Z = 1.24 (P = 0.22) 1.1.5 Bradycardia Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Sun2012 2 100 1 100 0.4% 2.00 [0.18, 21.71] Unlugenc2009 1 30 0 30 0.2% 3.00 [0.13, 70.83] Subtotal (95% Cl) 171 1 170 0.8% 4.45 [0.97, 20.36] Total events 8 1 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.24); P = 0% Test for overall effect: Z = 1.93 (P = 0.24); P = 0% Test for overall effect: Z = 1.93 (P = 0.24); P = 13% Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 43.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23); P = 0.05) End or subrotau (dffsmcccc); Ch <sup>2</sup> = 1.477. df = 4 (P = 0.005); P = 72.9%	Subtotal (95% CI)		430		393	19.4%	1.08 [0.76, 1.54]	<b>•</b>
Heterogenetiy: Ch <sup>2</sup> = 5.80, df = 9 (P = 0.76); P = 0% Test for overall effect: Z = 0.45 (P = 0.65) 1.1.4 Puritus Elsharkawy2018 0 30 2 30 1.0% 0.20 [0.01, 4.00] Malleeswaran2010 12 30 19 30 7.6% 0.63 [0.38, 1.06] Sun2012 2 100 3 100 1.2% 0.67 [0.11, 3.90] Unlugenc2009 1 30 1 30 0.4% 1.00 [0.07, 15.26] Zhong2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Subtotal (95% Cl) 2 295 295 13.7% 0.77 [0.51, 1.17] Total events 2 6 34 Heterogenetiy: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.83); P = 0% Test for overall effect: Z = 1.24 (P = 0.22) 1.1.5 Bradycardia Sachidananda2018 5 41 0 40 0.2% 3.00 [0.13, 70.83] Subtotal (95% Cl) 171 170 0.8% 4.45 [0.97, 20.36] Total events 8 1 Heterogenetiy: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); P = 0% Test for overall effect: Z = 1.93 (P = 0.21) 1.1.6 Respiratory depression Unlugenc2009 0 30 0 30 Not estimable Xiao2017 0 330 0 30 Not estimable Xiao2017 0 330 0 30 Not estimable Total events 2 49 240 Heterogenetiy: Ch <sup>2</sup> = 43.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23); P = 13% Test for overall effect: Z = 1.19 (P = 0.23); P = 12.9%.	Total events	55		48				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Heterogeneity: Chi <sup>2</sup> = :	5.80, df = 1	9 (P = 0	.76); l² =	0%			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	rest for overall effect:	2 = 0.45 (	P = 0.65	)				
Elsharkawy2018 0 30 2 30 1.0% 0.20 [0.01, 4.00] Malleeswaran2010 12 30 19 30 7.6% 0.63 [0.38, 1.06] Sun2012 2 100 3 100 1.2% 0.67 [0.11, 3.90] Unlugenc2009 1 30 1 30 0.4% 1.00 [0.07, 15.26] Xiao2017 8 30 7 30 2.8% 1.14 [0.47, 2.75] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Zhong2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Subtotal (95% CI) 295 295 13.7% 0.77 [0.51, 1.17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.83); P = 0% Test for overall effect: Z = 1.24 (P = 0.22) 1.1.5 Bradycardia Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Subtotal (95% CI) 171 170 0.8% 4.45 [0.97, 20.36] Total events 8 8 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.05); F = 0% Test for overall effect: Z = 1.93 (P = 0.23) 1.1.6 Respiratory depression Unlugenc2009 0 30 0 30 Not estimable Xiao2017 0 30 0 30 Not estimable Total (95% CI) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 249 240 Heterogeneity: Not applicable Total (95% CI) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 43.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.99 (P = 0.23) Favours [MgSC4] Favours [control]	1.1.4 Pruritus							
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Elsharkawy2018	0	30	2	30	1.0%	0.20 [0.01, 4.00]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Malleeswaran2010	12	30	19	30	7.6%	0.63 [0.38, 1.06]	
Unlugenc2009 1 30 1 30 0.4% 1.00 [0.07, 15.26] Xiao2017 8 30 7 30 2.8% 1.14 [0.47, 2.75] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Zhong2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Subtotal (95% CI) 295 295 13.7% 0.77 [0.51, 1.17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.83); P = 0% Test for overall effect: Z = 1.24 (P = 0.22) 1.1.5 Bradycardia Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Subtotal (95% CI) 171 170 0.8% 4.45 [0.97, 20.36] Total events 8 1 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.33 (P = 0.65); P = 0% Test for overall effect: Z = 1.33 (P = 0.65); P = 0% Test for overall effect: Z = 1.33 (P = 0.65); P = 0% Test for overall effect: Z = 1.33 (P = 0.65); P = 0% Test for overall effect: Z = 1.33 (P = 0.65); P = 0% Total events 8 1 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.33 (P = 0.65); P = 0% Total events 0 0 0 Heterogeneity: Not applicable Total (95% CI) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 249 240 Heterogeneity: Not applicable Total (95% CI) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 4.3.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Favours [MgSO4] Favours [Control]	Sun2012	2	100	3	100	1.2%	0.67 [0.11, 3.90]	
Xiac2017 8 30 7 30 2.8% 1.14 [0.47, 2.75] Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Zhong2018 1 30 1 30 0.4% 2.00 [0.19, 21.28] Subtotal (95% CI) 295 295 13.7% 0.77 [0.51, 1.17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.83); P = 0% Test for overall effect: Z = 1.24 (P = 0.22) 1.1.5 Bradycardia Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Sun2012 2 100 1 100 0.4% 2.00 [0.18, 21.71] Unlugenc2009 1 30 0 30 0.2% 3.00 [0.13, 70.83] Subtotal (95% CI) 171 170 0.8% 4.45 [0.97, 20.36] Total events 8 1 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.05) 1.1.6 Respiratory depression Unlugenc2009 0 30 0 30 Not estimable Xiac2017 0 30 0 30 Not estimable Xiac2017 0 30 0 30 Not estimable Subtotal (95% CI) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 0 0 0 Heterogeneity: Not applicable Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 43.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.93 (P = 0.24) Heterogeneity: Ch <sup>2</sup> = 4.3.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.19 (P = 0.23) Test for suboroun differences: Ch <sup>2</sup> = 1.4.77. df = 4 (P = 0.005), P = 72.9%	Unlugenc2009	1	30	1	30	0.4%	1.00 [0.07, 15.26]	
Yousef2010 2 45 1 45 0.4% 2.00 [0.19, 21.28] Zhong2018 1 30 1 30 0.4% 1.00 [0.07, 15.26] Subtotal (95% Cl) 295 295 13.7% 0.77 [0.51, 1.17] Total events 26 34 Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 ( $P = 0.83$ ); $P = 0\%$ Test for overall effect: Z = 1.24 ( $P = 0.22$ ) 1.1.5 Bradycardia Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Sun2012 2 100 1 100 0.4% 2.00 [0.18, 21.71] Unlugenc2009 1 30 0 30 0.2% 3.00 [0.13, 70.83] Subtotal (95% Cl) 171 170 0.8% 4.45 [0.97, 20.36] Total events 8 1 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 ( $P = 0.65$ ); $P = 0\%$ Test for overall effect: Z = 1.93 ( $P = 0.05$ ) 1.1.6 Respiratory depression Unlugenc2009 0 30 0 30 Not estimable Xiao2017 0 30 0 30 Not estimable Subtotal (95% Cl) 60 60 Not estimable Total (95% Cl) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 0 0 0 Heterogeneity: Not applicable Total (95% Cl) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 4.3.91, df = 38 ( $P = 0.23$ ); $P = 13\%$ Test for overall effect: Z = 1.19 ( $P = 0.23$ ) Test for overall effect: Z = 1.93 ( $P = 0.23$ ); $P = 72.9\%$	Xiao2017	8	30	7	30	2.8%	1.14 [0.47, 2.75]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Yousef2010	2	45	1	45	0.4%	2.00 [0.19, 21.28]	
$\begin{array}{c} \text{Loss in (b), b)} & \text{Loss in (b), b)} \\ \text{Total events} & 26 & 34 \\ \text{Heterogeneity: } \text{Ch}^2 = 2.84, \text{ df} = 6 (P = 0.83); P = 0\% \\ \text{Test for overall effect: } Z = 1.24 (P = 0.22) \\ \hline 1.1.5 \text{ Bradycardia} \\ \text{Sachidananda2018} & 5 & 41 & 0 & 40 & 0.2\% & 10.74 [0.61, 188.05] \\ \text{Sun2012} & 2 & 100 & 1 & 100 & 0.4\% & 2.00 [0.18, 21.71] \\ \text{Unlugenc2009} & 1 & 30 & 0 & 30 & 0.2\% & 3.00 [0.13, 70.83] \\ \text{Subtotal (95\% CI)} & 171 & 177 & 0.8\% & 4.45 [0.97, 20.36] \\ \hline \text{Total events} & 8 & 1 \\ \text{Heterogeneity: Chi^2 = 0.86, df = 2 (P = 0.65); P = 0\% \\ \text{Test for overall effect: Z = 1.93 (P = 0.05)} \\ \hline 1.1.6 \text{ Respiratory depression} \\ \text{Unlugenc2009} & 0 & 30 & 0 & 30 & \text{Not estimable} \\ \text{Subtotal (95\% CI)} & 60 & 60 & \text{Not estimable} \\ \text{Subtotal (95\% CI)} & 60 & 60 & \text{Not estimable} \\ \text{Subtotal (95\% CI)} & 1797 & 1685 & 100.0\% & 0.91 [0.78, 1.06] \\ \hline \text{Total events} & 249 & 240 \\ \text{Heterogeneity: Chi^2 = 4.3.91, df = 38 (P = 0.24); P = 13\% \\ \text{Test for overall effect: Z = 1.19 (P = 0.23)} \\ \hline \text{Test for overall effect: Z = 1.19 (P = 0.23)} \\ \hline \text{Test for overall effect: Z = 1.19 (P = 0.23)} \\ \hline \text{Favours [MgSO4] Favours [control]} \\ \hline \end{array}$	Subtotal (95% CI)	1	295	1	295	13.7%	0 77 [0 51 1 17]	•
Heterogeneity: Ch <sup>2</sup> = 2.84, df = 6 (P = 0.83); P = 0% Test for overall effect: $Z = 1.24$ (P = 0.22) <b>1.1.5 Bradycardia</b> Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Sun2012 2 1 00 1 100 0.4% 2.00 [0.18, 21.71] Unlugenc2009 1 30 0 30 0.2% 3.00 [0.13, 70.83] Subtotal (95% Cl) 171 170 0.8% 4.45 [0.97, 20.36] Total events 8 1 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: $Z = 1.93$ (P = 0.05) <b>1.1.6 Respiratory depression</b> Unlugenc2009 0 30 0 30 Not estimable Xiao2017 0 30 0 30 Not estimable Subtotal (95% Cl) 60 60 Not estimable Total events 0 0 0 Heterogeneity: Not applicable Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 4.3.91, df = 38 (P = 0.24); P = 13% Test for overall effect: $Z = 1.19$ (P = 0.23) Test for overall effect: $Z = 1.477$ . df = 4 (P = 0.005), P = 72.9%	Total events	26		34				-
Test for overall effect: $Z = 1.24$ (P = 0.22) <b>1.1.5</b> Bradycardia Sachidananda2018 5 41 0 40 0.2% 10.74 [0.61, 188.05] Sun2012 2 100 1 100 0.4% 2.00 [0.18, 21.71] Unlugenc2009 1 30 0 30 0.2% 3.00 [0.13, 70.83] Subtotal (95% CI) 171 170 0.8% 4.45 [0.97, 20.36] Total events 8 1 Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0% Test for overall effect: Z = 1.93 (P = 0.05) <b>1.1.6</b> Respiratory depression Unlugenc2009 0 30 0 30 Not estimable Xiao2017 0 30 0 30 Not estimable Subtotal (95% CI) 60 60 Not estimable Total events 0 0 0 Heterogeneity: Not applicable Total events 249 240 Heterogeneity: Ch <sup>2</sup> = 43.91, df = 38 (P = 0.24); P = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for overall effect: Z = 1.93 (P = 0.24); P = 13% Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for overall effect: Z = 1.9 (P = 0.23) Test for suboroun differences: Ch <sup>2</sup> = 1.4.77. df = 4 (P = 0.005), P = 72.9%	Heterogeneity: Chi <sup>2</sup> = 2	2.84, df =	6 (P = 0	.83); l <sup>2</sup> =	0%			
1.1.5 Bradycardia         Sachidananda2018       5       41       0       40       0.2%       10.74 [0.61, 188.05]         Sun2012       2       100       1       100       0.4%       2.00 [0.18, 21.71]         Unlugenc2009       1       30       0       30       0.2%       3.00 [0.13, 70.83]         Subtotal (95% CI)       171       170       0.8%       4.45 [0.57, 20.36]         Total events       8       1         Heterogeneity: Chi# = 0.86, df = 2 (P = 0.65); P = 0%         Test for overall effect: Z = 1.93 (P = 0.05)         1.1.6 Respiratory depression         Unlugenc2009       0       30       0       30         Subtotal (95% CI)       60       60       Not estimable         Subtotal (95% CI)       0       0       0         Heterogeneity: Not applicable       Total (95% CI)       1797       1685       100.0%       0.91 [0.78, 1.06]         Total (95% CI)       1797       1685       100.0%       0.91 [0.78, 1.06]       0.01       0.1       10         Fast for overall effect: Z = 1.19 (P = 0.23);       179       1685       100.0%       0.91 [0.78, 1.06]       100         Total events       249       240       -0.01	Test for overall effect:	Z = 1.24 (	P = 0.22	)				
1.1.5 Braygearoia         Sachidananda2018       5       41       0       40       0.2%       10.74 [0.61, 188.05]         Subidananda2018       5       41       0       40       0.2%       10.74 [0.61, 188.05]         Subidananda2018       5       41       0       0.4%       2.00 [0.18, 21.71]         Unlugenc2009       1       30       0       30       0.2%       3.00 [0.13, 70.83]         Subtotal (95% CI)       171       170       0.8%       4.45 [0.97, 20.36]       1         Total events       8       1       1       1       1         Heterogeneity: Chi <sup>p</sup> = 0.86, df = 2 (P = 0.65); P = 0%       1       1       1         Unlugenc2009       0       30       0.30       Not estimable         Subtotal (95% CI)       60       60       Not estimable         Total events       249       240       1         Heterogeneity: Chi <sup>p</sup> = 43.91, df = 38 (P = 0.24); P = 13%       0.01       0.1       1       10         Total events       249       240       240       1       10       100         Favours [MgSO4]       Favours [MgSO4]       Favours [MgSO4]       Favours [MgSO4]       Favours [MgSO4]	445 Decider and							
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.1.5 Bradycardia	~	44	~	40	0.00/	10 74 10 64 400 053	<b>`</b>
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Sachidananda2018	5	41	0	40	0.2%	2 00 [0 19 21 74]	
Subtotal (95% Cl)       171       170       0.8%       4.45 [0.97, 20.36]         Total events       8       1         Heterogeneity: Ch <sup>2</sup> = 0.86, df = 2 (P = 0.65); P = 0%         Test for overall effect: Z = 1.93 (P = 0.05)         1.1.6 Respiratory depression         Unlugenc2009       0       30       Not estimable         Subtotal (95% Cl)       60       60       Not estimable         Subtotal (95% Cl)       60       60       Not estimable         Total events       0       0       Heterogeneity: Not applicable         Total (95% Cl)       1797       1685       100.0%       0.91 [0.78, 1.06]         Total events       249       240       4.45 [0.97, 20.36]       4.45 [0.97, 20.36]         Heterogeneity: Ch <sup>2</sup> = 4.3.91, df = 38 (P = 0.24); P = 13%       0.01       0.1       1       100         Fast for overall effect: Z = 1.1.9 (P = 0.23)       Favours [MgSO4]       Favours [MgSO4]       Favours [MgSO4]       Favours [Control]	Unlugenc2009	2	30	0	30	0.4%	3 00 [0.13, 70 83]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Subtotal (95% CI)		171	0	170	0.8%	4.45 [0.97, 20.36]	
$ \begin{array}{c} \mbox{Heterogeneity: Chi^2 = 0.86, df = 2 (P = 0.65); P = 0\% \\ \mbox{Test for overall effect: Z = 1.93 (P = 0.05) \\ \hline \mbox{I.1.6 Respiratory depression} \\ \mbox{Unlugenc2009} & 0 & 30 & 0 & 30 & Not estimable \\ \mbox{Subtotal (95% Cl)} & 0 & 0 & 0 \\ \mbox{Subtotal (95% Cl)} & 60 & 60 & Not estimable \\ \mbox{Total events} & 0 & 0 & 0 \\ \mbox{Heterogeneity: Chi^2 = 43.91, df = 38 (P = 0.24); P = 13\% \\ \mbox{Test for overall effect: Z = 1.19 (P = 0.23) \\ \mbox{Test for overall effect: Z = 1.19 (P = 0.23) \\ \mbox{Test for overall effect: Chi^2 = 14.77. df = 4 (P = 0.005), P = 72.9\% \\ \end{array} $	Total events	8		1				
Test for overall effect: Z = 1.93 (P = 0.05) <b>1.1.6 Respiratory depression</b> Unlugenc2009       0       30       0       Not estimable         Xiao2017       0       30       0       Not estimable         Subtotal (95% CI)       60       60       Not estimable         Total (95% CI)       1797       1685       100.0%       0.91 [0.78, 1.06]         Total (95% CI)       1797       1685       100.0%       0.91 [0.78, 1.06]         Total (95% CI)       1797       1685       100.0%       0.91 [0.78, 1.06]         Total (95% CI)       1797       1685       100.1       1       10         Total (95% CI)       1797       1685       100.1       1       10         Total events       249       240       0.91 [0.78, 1.06]       90         Test for overall effect: Z = 1.19 (P = 0.23)       0.01       0.1       1       100         Test for overall effect: Z = 1.19 (P = 0.23)       Favours [MgSO4]       Favours [MgSO4]       Favours [Control]	Heterogeneity: Chi <sup>2</sup> =	0.86, df = :	2 (P = 0	.65); l² =	0%			
1.1.6 Respiratory depression         Unlugenc2009       0       30       0       30       Not estimable         Xiao2017       0       30       0       30       Not estimable         Subtotal (95% CI)       60       60       Not estimable         Total events       0       0         Heterogeneity: Not applicable       Total (95% CI)       1797       1685       100.0%       0.91 [0.78, 1.06]         Total (95% CI)       1797       1685       100.0%       0.91 [0.78, 1.06]       0.01       0.1       1       10         Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); I <sup>2</sup> = 13%       0.01       0.1       1       10       100         Test for overall effect: Z = 1.1 91 (P = 0.23)       Test for subcroup differences: Chi <sup>2</sup> = 14.77. df = 4 (P = 0.005), I <sup>2</sup> = 72.9%       Favours [MgSO4]       Favours [Control]	Test for overall effect:	Z = 1.93 (	P = 0.05	)				
Total pression       0       30       0       30       Not estimable         Xiao2017       0       30       0       30       Not estimable         Subtotal (95% Cl)       60       60       Not estimable         Total events       0       0         Heterogeneity: Not applicable       Total events       249       240         Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); l <sup>2</sup> = 13%       0.01       0.1       100         Test for overall effect: Z = 1.19 (P = 0.23)       Favours [MgSO4]       Favours [MgSO4]       Favours [MgSO4]	116 Respiratory dor	ression						
Child Statute         Column Statute         Column Statute         Column Statute           Subtotal (95% Cl)         60         60         Not estimable           Total events         0         0         0           Heterogeneity: Not applicable         Total (95% Cl)         1797         1685         100.0%         0.91 [0.78, 1.06]           Total events         249         240         240         100         100           Test for overall effect: Z = 1.19 (P = 0.23)         138 (P = 0.24); I <sup>2</sup> = 13%         0.01         0.1         1         100           Test for overall effect: Z = 1.19 (P = 0.23)         Favours [MgSO4]         Favours [MgSO4]         Favours [MgSO4]         Favours [Control]	Linkugenc2000	nession ^	30	0	30		Not estimable	
Subtotal (95% Cl)         60         60         Not estimable           Total events         0         0           Heterogeneity: Not applicable         Total (95% Cl)         1797           Total (95% Cl)         1797         1685           Total events         249         240           Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); l <sup>2</sup> = 13%         0.01         0.1           Test for overall effect: Z = 1.1 9 (P = 0.23)         Pavours [MgSO4]         Favours [MgSO4]           Favours [MgSO4]         Favours [Control]         Favours [Control]	Xiao2017	0	30	0	30		Not estimable	
Total events       0       0         Heterogeneity: Not applicable       Test for overall effect: Not applicable         Total (95% Cl)       1797       1685       100.0%       0.91 [0.78, 1.06]         Total events       249       240         Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); l <sup>2</sup> = 13%       0.01       0.1       1       100         Test for overall effect:       1.19 (P = 0.23)       Favours [MgSC4]       Favours [Control]	Subtotal (95% CI)	5	60	5	60		Not estimable	
Heterogeneity: Not applicable Test for overall effect: Not applicable Total (95% Cl) 1797 1685 100.0% 0.91 [0.78, 1.06] Total events 249 240 Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); l <sup>2</sup> = 13% Test for overall effect: 2 = 1.19 (P = 0.23) Test for subaroup differences: Chi <sup>2</sup> = 14.77. df = 4 (P = 0.005). l <sup>2</sup> = 72.9% Favours [MgSO4] Favours [Control]	Total events	0		0				
Test for overall effect: Not applicable           Total (95% Cl)         1797         1685         100.0%         0.91 [0.78, 1.06]           Total events         249         240           Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); l <sup>2</sup> = 13%         0.01         0.1         100           Test for overall effect: Z = 1.19 (P = 0.23)         Favours [MgSO4]         Favours [MgSO4]         Favours [Control]	Heterogeneity: Not app	plicable						
Total (95% Cl)         1797         1685         100.0%         0.91 [0.78, 1.06]           Total events         249         240           Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); l <sup>2</sup> = 13%         0.01         0.1         1         100           Test for overall effect: Z = 1.19 (P = 0.23)         Favours [MgSO4]         Favours [MgSO4]         Favours [MgSO4]         Favours [MgSO4]	Test for overall effect:	Not applic	able					
Total events         249         240           Heterogeneity: Chi² = 43.91, df = 38 (P = 0.24); l² = 13%         0.01         0.1         1         100           Test for overall effect: Z = 1.19 (P = 0.23)         Favours [MgSO4]         Favours [MgSO4]         Favours [Control]	Total (95% CI)		1797		1625	100.0%	0 91 [0 78 1 061	4
Heterogeneity: Chi <sup>2</sup> = 43.91, df = 38 (P = 0.24); l <sup>2</sup> = 13% Test for overall effect: Z = 1.19 (P = 0.23) Test for subaroup differences: Chi <sup>2</sup> = 14.77. df = 4 (P = 0.005). l <sup>2</sup> = 72.9%	Total events	240	1131	240	1000	100.0%	0.01 [0.70, 1.00]	<b>"</b>
Test for overall effect: Z = 1.19 (P = 0.23)         0.01         0.1         1         100           Test for subaroup differences: Chi <sup>2</sup> = 14.77. df = 4 (P = 0.005). l <sup>2</sup> = 72.9%         Favours [MgSO4]         Favours [control]	Heterogeneity: Chi <sup>2</sup> = 4	43.91. df =	= 38 (P =	: 0.24): F	2 = 13%			
Test for subaroup differences: Chi <sup>2</sup> = 14.77. df = 4 (P = 0.005). l <sup>2</sup> = 72.9%	Test for overall effect:	Z = 1.19 (	P = 0.23	)				0.01 0.1 1 10 100
	Test for subaroup diffe	erences: C	hi² = 14.	77. df =	4 (P =	0.005). I²	= 72.9%	

Fig. 3 Adverse drug events observed with intrathecal magnesium sulfate as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section

	IV	lgSo4		С	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C		IV, Random, 95% Cl
2.1.1 Sensory block	onset									
Elsharkawy2018	16.65	0.84	30	20.06	0.78	30	5.1%	-3.41 [-3.82, -3.00]		•
Faiz2013	2.49	0.69	36	2.47	0.77	36	5.1%	0.02 [-0.32, 0.36]		•
Paleti2018	9.9	1.4	25	7.9	0.9	25	5.1%	2.00 [1.35, 2.65]		•
Xiao2017	4	0	30	3	0	30		Not estimable		
Yousef2010	6.3	1.2	45	6.7	1.1	45	5.1%	-0.40 [-0.88, 0.08]		•
Zhong2018	5.35	1.35	30	6.25	1.75	30	5.1%	-0.90 [-1.69, -0.11]		•
Subtotal (95% CI)			196			196	25.7%	-0.54 [-2.27, 1.18]		<b>+</b>
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	3.79; Cł Z = 0.62	ni² = 25 2 (P = 0	51.70, o ).54)	if = 4 (F	P < 0.0	0001);	<sup>2</sup> = 98%			
2.1.2 Sensory block	duration	1								
Faiz2013	80.42	4.98	36	77.36	4.99	36	5.1%	3.06 [0.76, 5.36]		-
Paleti2018	295	36	25	245	26.4	25	2.8%	50.00 [32.50, 67.50]		
Xiao2017	140	9	30	121	9	30	4.9%	19.00 [14.45, 23.55]		-
Zhong2018	261.3	64.7	30	226.5	56.4	30	1.4%	34.80 [4.09, 65,51]		
Subtotal (95% CI)			121			121	14.1%	23.15 [7.83, 38.48]		
Heterogeneity: Tau <sup>2</sup> =	189.98:	Chi² =	64.25.	df = 3 (	P < 0.0	00001)	: l² = 95%	)		
Test for overall effect:	Z = 2.96	6 (P = 0	0.003)			,				
2.1.3 Onset of motor	block									
Elsharkawy2018	4.35	1.4	30	5.15	1.3	30	5.1%	-0.80 [-1.48, -0.12]		•
Malleeswaran2010	5.7	0.7	30	5.1	1	30	5.1%	0.60 [0.16, 1.04]		•
Paleti2018	12.5	1.6	25	7.7	3.2	25	5.1%	4.80 [3.40, 6.20]		•
Xiao2017	4	0	30	2	0	30		Not estimable		
Zhong2018	4.15	0.95	30	4.5	1.05	30	5.1%	-0.35 [-0.86, 0.16]		+
Subtotal (95% CI)			145			145	20.5%	0.89 [-0.50, 2.27]		•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	1.82; Cł Z = 1.26	ni² = 57 δ (P = 0 κ	'.29, df ).21)	= 3 (P	< 0.00	001); l²	= 95%			
Addagest Annual Annua	200	n 170	20	175 0	10.2	20	4 20/	24 70 [46 66 22 94]		
Deleti2019	200	24.6	25	170.0	10.0	25	4.Z/0 2.50/	42.00 [20.04 54.00]		
Viao2017	1/0	24.0	20	125	22.Z	20	3.5%	42.00 [29.01, 54.99]		
Xid02017 Xoucof2010	140	26	30	120	24	30	4.7 %	23.00 [17.41, 20.39]		<u> </u>
7bong2019	104.6	25.4	20	127.9	27.0	20	3.2%	19 00 [2 77 25.02]		
Subtotal (95% CI)	194.0	55.4	160	175.7	27.9	160	3.0%	24 29 116 36 32 231		•
Heterogeneity: Tau <sup>2</sup> =	48.52; 0	Chi² = 1	0.96, c	lf = 4 (F	P = 0.03	3); I <sup>2</sup> =	64%	24.20 [10.00, 02.20]		•
Test for overall effect:	Z = 6.00	) (P < (	00001	)						
2.1.5 Time to first rec	quest of	analg	esia							
Elsharkawy2018	388.2	8.8	30	172.4	8.1	30	4.9%	215.80 [211.52, 220.08]		F
Paleti2018	334	39	25	280	23.4	25	2.7%	54.00 [36.17, 71.83]		
Subtotal (95% CI)			55			55	7.6%	135.14 [-23.42, 293.70]		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	13045.8 Z = 1.67	36; Chi <sup>2</sup> 7 (P = 0	² = 299 ).09)	.15, df =	= 1 (P ·	< 0.000	01); l² = ·	100%		
2.1.6 Duration of spin	nal anes	thesia								
Malleeswaran2010	229.3	15.1	30	187.7	11	30	4.6%	41.60 [34.91, 48.29]		· -
Xiao2017	183	11	30	148	9	30	4.8%	35.00 [29.91, 40.09]		
Zhong2018 Subtotal (95% CI)	81.5	18.6	30 <b>90</b>	71.4	16.5	30 <b>90</b>	4.2% <b>13.6%</b>	10.10 [1.20, 19.00] <b>29.24 [13.61, 44.87</b> ]		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	178.04; Z = 3.67	Chi² = ' (P = 0	32.38, ).0002)	df = 2 (	(P < 0.0	00001)	;  ² = 94%	-		
			767			767	100 00/	22 54 [40 26 27 22]		
Heterogeneity: Tau <sup>2</sup> -	03 10. 0	<sup>-</sup> hi <sup>2</sup> – 1	0756	IQ df –	22 /D		01). 12 -	100%	H	
Test for overall effect:	Z = 10.7	76 (P <	0.0000	)1)	22 (P '	~ 0.000	, I <sup>-</sup> =	100 /o	-100	-50 0 50 100 Favours [control] Favours [MgSO4]
Test for subaroup diffe	erences:	Chi <sup>2</sup> =	59.52.	df = 5 (	P < 0.0	00001)	$I^2 = 91.6$	1%		

Fig. 4 Efficacy outcomes observed with intrathecal magnesium sulfate as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section



Fig. 5 Funnel plot showing publication bias

#### Table 4 Results of this analysis

Endpoints related to the adverse drug reactions	RR with 95% Cl	P value	l <sup>2</sup> value (%)	
Shivering	0.63 [0.48 – 0.83]	0.001	33	
Hypotension	1.11 [0.86 – 1.44]	0.40	0	
Nausea and vomiting	1.08 [0.76 – 1.54]	0.65	0	
Pruritus	0.77 [0.51 – 1.17]	0.22	0	
Bradycardia	4.45 [0.97 – 20.36]	0.05	0	
Endpoints related to the efficacy outcomes	WMD with 95% Cl	P value	l <sup>2</sup> value (%)	
Sensory block onset	-0.54 [-2.27 - 1.18]	0.54	98	
Sensory block duration	23.15 [7.83 – 38.48]	0.003	95	
Motor block onset	0.89 [-0.50 - 2.27]	0.21	95	
Motor block duration	24.29 [16.36 – 32.23]	0.00001	64	
Time to first request of analgesia	135.14 [-23.42 - 293.70]	0.09	100	
Duration of spinal anesthesia	29.24 [13.61 – 44.87]	0.0002	94	

The results of this current analysis have been summarized in Table 4. Risk ratios with 95% confidence intervals were used to represent the results related to the adverse drug reactions whereas weighted mean difference was used to represent the results related to the efficacy outcomes

Abbreviations: RR: Risk ratios; CI: Confidence intervals; WMD: Weighted mean difference

of spinal anesthesia was significantly longer with intrathecal MgSO4 when compared to the control group.

In another study, MgSO4 was added to ropivacaine in local infiltration for post-operative pain following cesarean section [23]. Results of the study showed the analgesic effects to have been prolonged without any increase in adverse effects. Similarly, in a retrospective analysis [24], whereby 32 patients received MgSO4 infusion after cesarean section, the authors demonstrated that MgSO4 decreased total analgesic requirements and pain during the first 24 hrs after surgery.

In our analysis, MgSO4 significantly reduced the risk of shivering. In another double-blind controlled study [13], the latter reported similar result as shown in this analysis by reducing the risk of shivering peri-operatively. Other studies have shown intravenous MgSO4 to be beneficial post-operatively following any surgery highlighting the potential of MgSO4 as a valuable adjunct for multimodal anesthesia and enhanced recovery [25]. The mechanism that causes shivering following administration of spinal anesthesia is related to the vasodilatation of vessels, which in turn, facilitates rapid heat loss therefore causing a redistribution of heat from the core to peripheral tissues, ending with shivering [26]. Other mechanisms could be related to reflexes of spinal cord, reduction of sympathetic stimulation, inhibition of the adrenal gland, pyrogenic production and post-surgical pain [27]. MgSO4 induces thermoregulation tolerance which could explain how it reduced shivering in patients post spinal anesthesia [28]. Prevention of shivering by magnesium could also be explained by its ability to modulate serotoninergic and noradrenergic neurons enhancing to the effect of N-methyl-D aspartate receptors in the dorsal raphe nucleus [29], and also decreases the gain of shivering by peripheral muscle relaxation via calcium antagonist [30]. The lowest recommended and effective dosage of intravenous MgSO4 is 50 mg/kg for the prevention and treatment of shivering without any significant adverse event [31].

The efficacy of MgSO4 as adjuvant to the anesthetic agent has been proven in several studies. When compared to a control group, intrathecal MgSO4 could prolong the duration of spinal anesthesia without causing any rise in adverse drug events thus favoring its use [20]. Another example showing better efficacy of intrathecal MgSO4 following cesarean section was the fact its use prolonged the duration of sensory and motor nerve blocks as well as the duration of spinal anesthesia without any significant adverse events [22].

However, other studies showed different results. For example, a randomized, prospective, double-blind, casecontrol clinical trial based on the addition of intrathecal MgSO4 to bupivacaine for spinal anesthesia in cesarean section did not show desirable outcomes due to the delayed onset of sensory blockade and the reduced effects of MgSO4 on post-operative pain [32]. In addition, there are other more potent drugs. Intrathecal dexmedetomidine showed superiority to intrathecal MgSO4 based on analgesia duration, severity of pain, onset duration, and duration of effects of the drug during cesarean section [33]. In a double-blind randomized clinical trial, where the effects of intrathecal dexmedetomidine versus MgSO4 were compared following cesarean delivery [34], the former showed to have a better effect on reducing shivering and its severity post-operatively demonstrating that dexmedetomidine might be a better option than MgSO4.

### Limitations

One major limitation is the fact that the total number of participants was less compared to other studies. However, less research has been carried out based on this scope and since our task was to collect data on previously published studies, we could only extract whatever data are available. Publication bias which has been observed across the studies that were involved in carrving out this analysis could also be a limitation of this analysis. Another limitation could be the fact that several outcomes such as respiratory depression and dizziness were reported in only one study and therefore, the data for that specific outcome could not be used for comparison. In addition, a higher heterogeneity was observed during analysis of the efficacy outcomes and this could be another limitation. Moreover, even though registration of manuscript is not compulsory, this manuscript was not registered with PROSPERO during its protocol stage. This could also be a limitation of this study.

# Conclusions

Intrathecal MgSO4 as an adjuvant to bupivacaine was associated with a significantly lower risk of shivering without causing any increase in other adverse drug events in patients undergoing elective cesarean section. Efficacy outcomes were also appreciated. Larger studies should be able to confirm this hypothesis.

#### Abbreviations

MgSO4Magnesium sulfateSASpinal anesthesiaCSCesarean section

#### Acknowledgements

Not applicable.

### Author contributions

Dr Yuanhui Zhang, Dr Yan Huang, and Dr Jun Li were responsible for the conception and design, drafting the initial manuscript and revising it critically for important intellectual content. Dr Yuanhui Zhang and Dr Yan Huang wrote the final draft. All the authors approved the final manuscript as it has been written.

#### Funding

There was no external source of funding for this research. This research was funded by the authors.

#### Data availability

All data and materials used in this research are freely available in electronic databases (MEDLINE, EMBASE, http://www.ClinicalTrials.gov, Web of Science, Cochrane database, Google scholar). References have been provided.

### Declarations

### Ethics approval and consent to participate

Ethical approval was not applicable for this systematic review and meta-analysis.

#### **Clinical trial number**

Not applicable.

#### **Consent for publication**

Not applicable.

# Consent to participate

Not applicable.

#### **Competing interests**

The authors declare no competing interests.

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### Received: 5 November 2024 / Accepted: 23 April 2025 Published online: 06 May 2025

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