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Adverse drug events observed with intrathecal magnesium sulfate as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section: a meta-analysis

Yuanhui Zhang[1†], Yan Huang[2†] and Jun Li[3*]

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 (CIs) were used to represent analysis for the dichotomous data whereas weighted mean difference (WMD) with 95% CI was used to represent results using continuous data. Heterogeneity was assessed by the Q statistic and the I2 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, 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.

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^2 statistic test whereby a subgroup analysis with an I^2 value less than 50% was considered to have a low heterogeneity and a subgroup analysis with an I^2 value greater than 50% was considered to have a higher heterogeneity. A fixed effect statistical model was used for lower heterogeneity ($I^2 < 50\%$) whereas a random effect statistical model was used for an increasing I^2 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

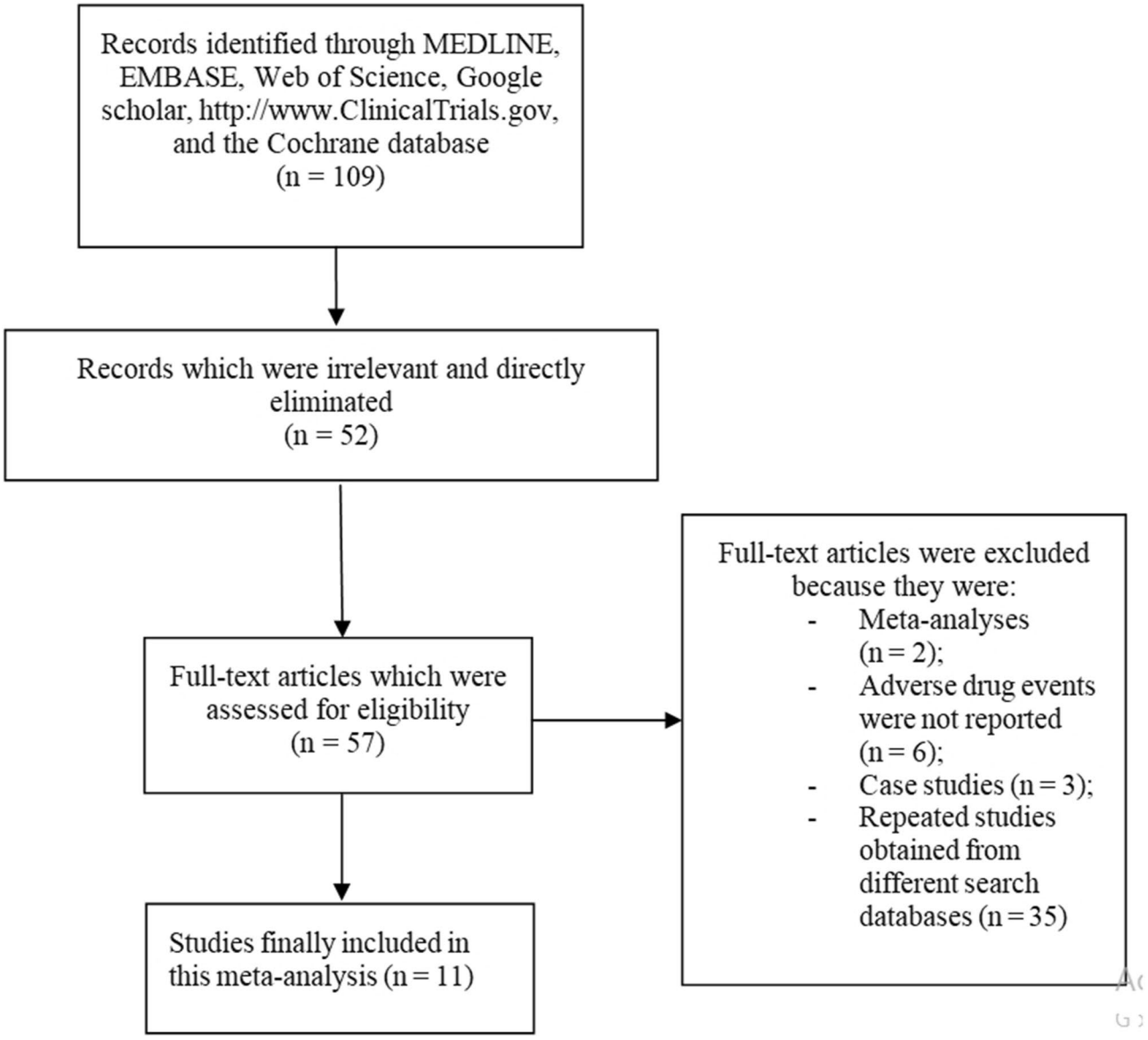

Fig. 1 Flow diagram showing the study selection for this analysis

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 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; $p = 0.00001$) 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

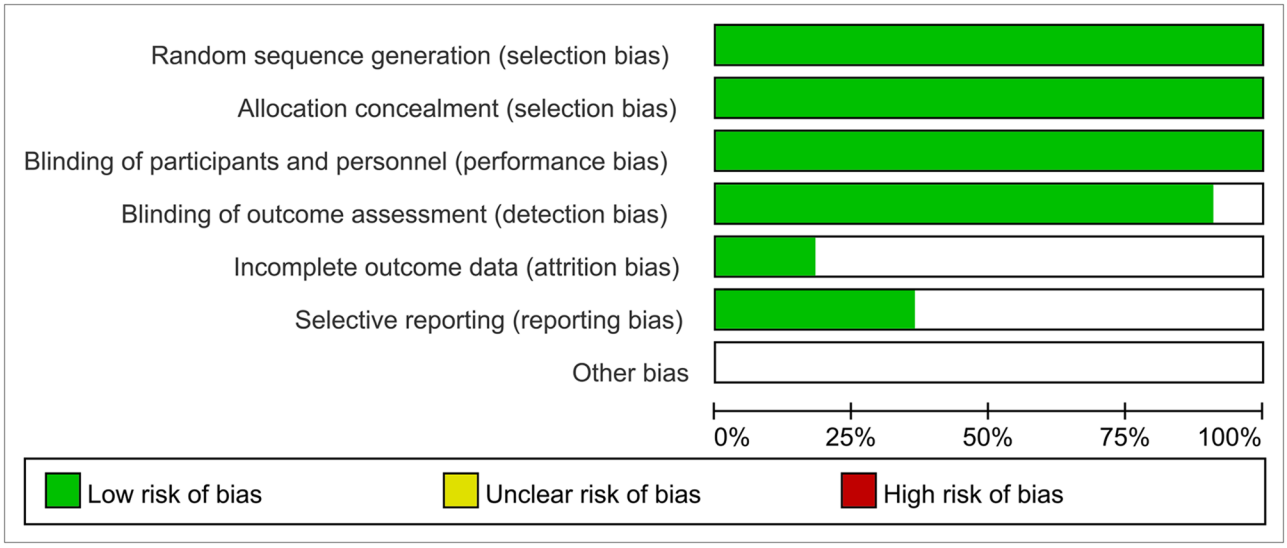

Fig. 2 Risk of bias assessment

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 (minute), time for complete motor block (minute), pain free period (minute), number of patients needing supplementary analgesics, total post operative 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 (μg)	Hypotension, nausea and vomiting, shivering, pruritus, severe sedation, respiratory 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, intraoperative pain or discomfort, post-operative 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 vomiting, 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 participants 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^2)	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 [16]	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 [20]	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^2: 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

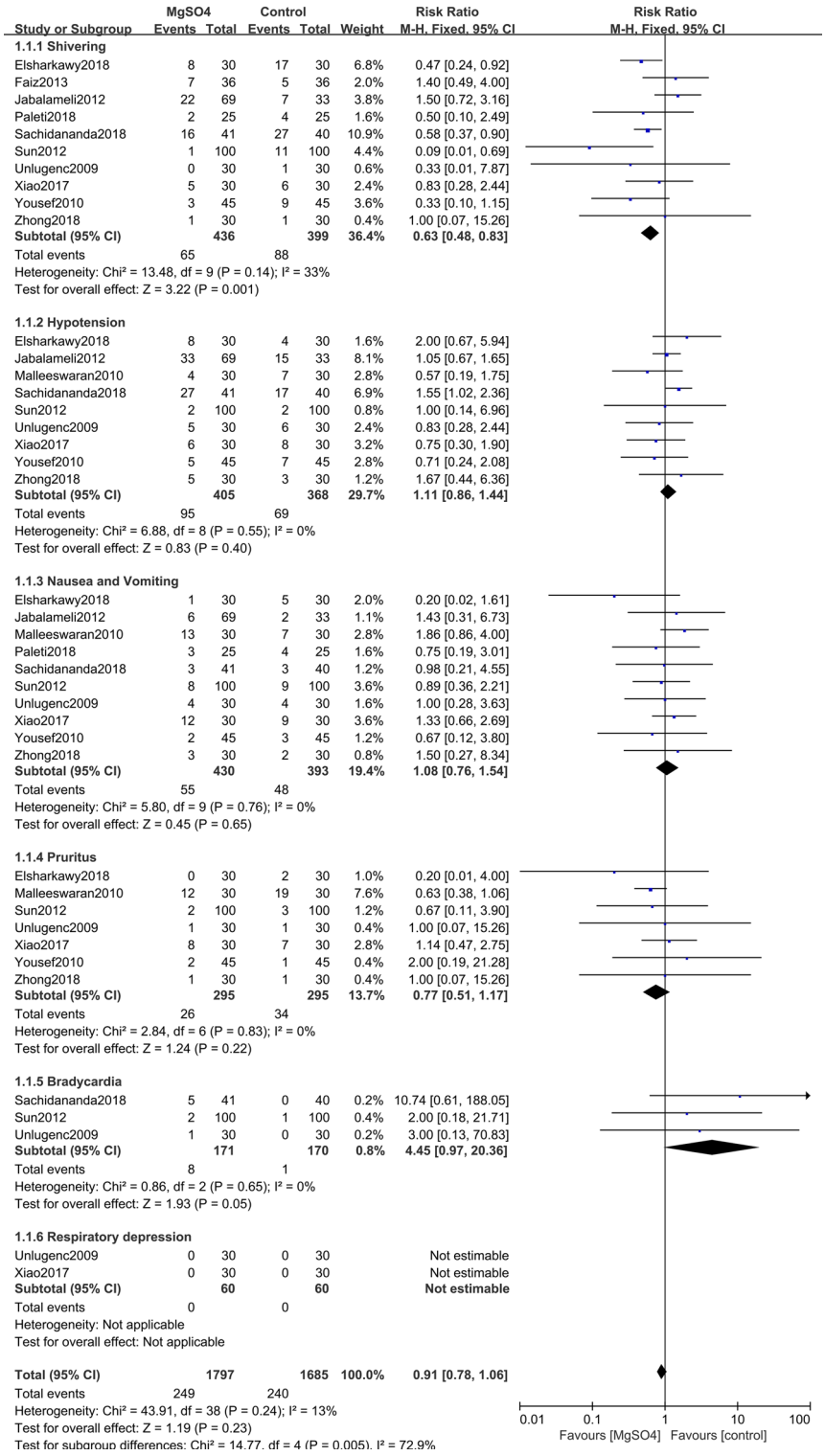

Fig. 3 Adverse drug events observed with intrathecal magnesium sulfate as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section

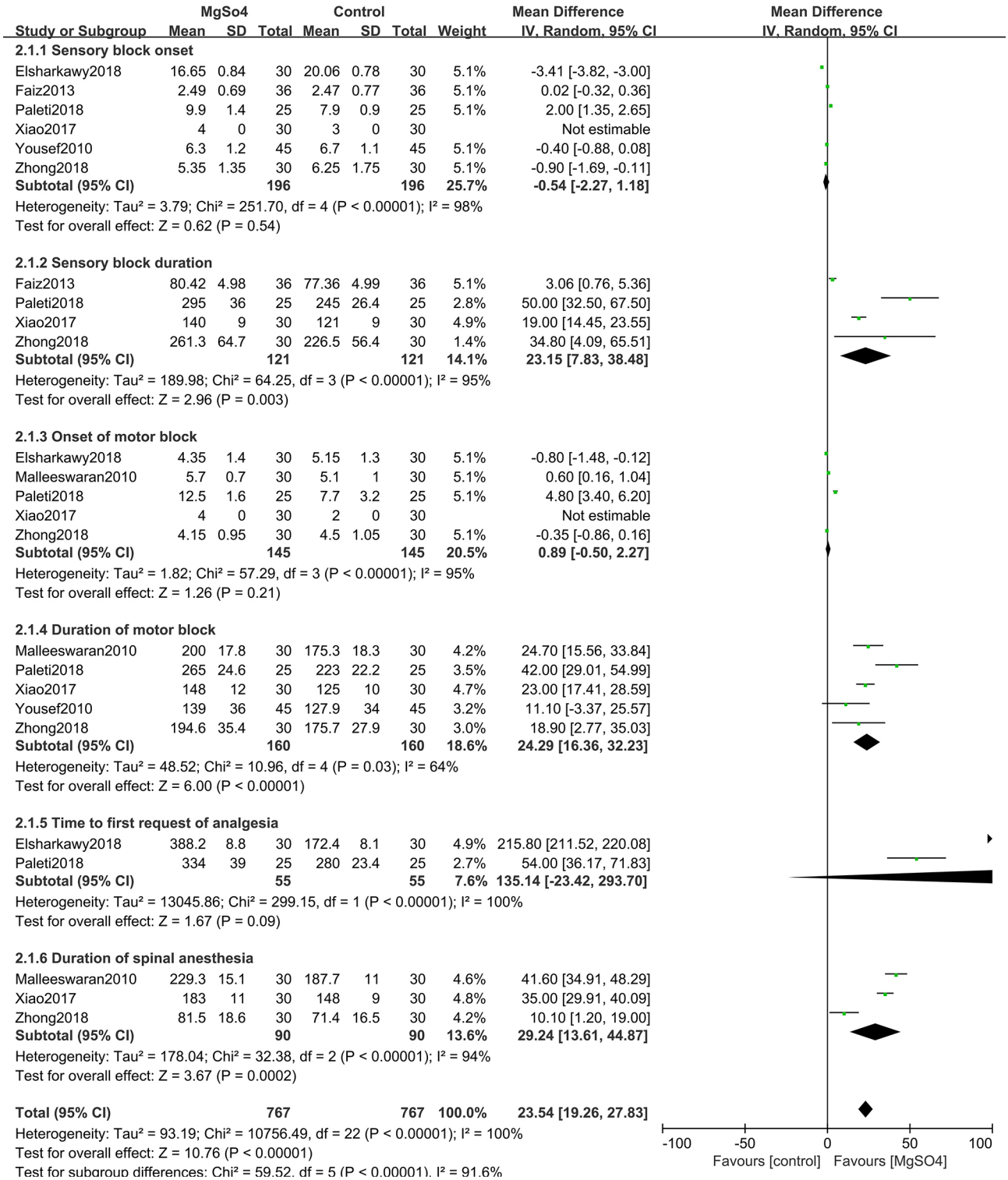

Fig. 4 Efficacy outcomes observed with intrathecal magnesium sulfate as an adjuvant to bupivacaine for spinal anesthesia in patients undergoing elective cesarean section

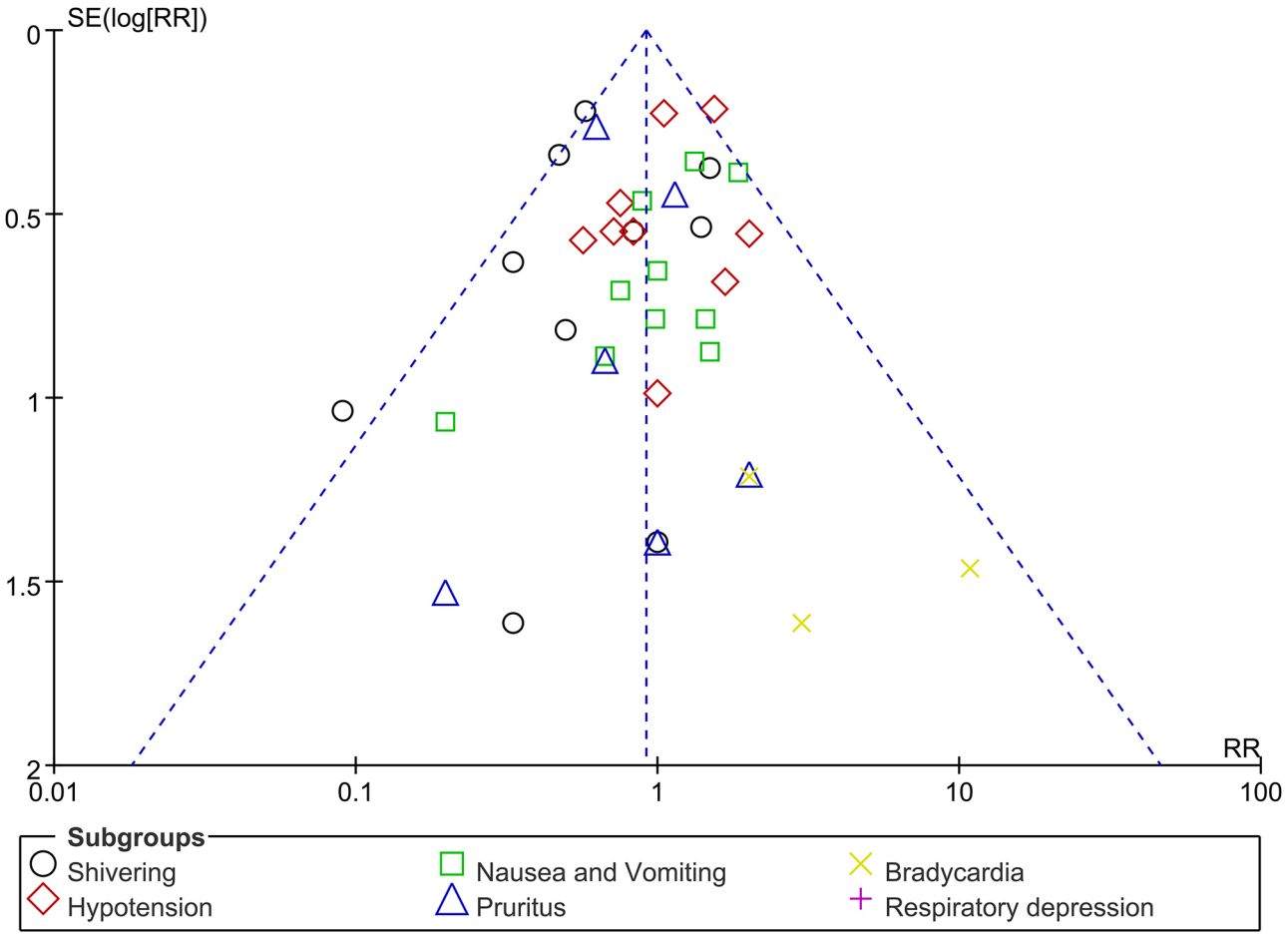

Fig. 5 Funnel plot showing publication bias

Table 4 Results of this analysis

Endpoints related to the adverse drug reactions	RR with 95% CI	P value	I^2 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% CI**	**P value**	**I^2value (%)**
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, case-control 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 carrying 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

MgSO4	Magnesium sulfate
SA	Spinal anesthesia
CS	Cesarean section

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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.

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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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References

1. Küçük M. Striking rise of cesarean section rates in Türkiye: There is a need for a whole new perspective. Pan Afr Med J. 2024 May 3;48:6.
2. Murphy SL, Mathews TJ, Martin JA, Minkovitz CS, Strobino DM. Annual summary of vital statistics: 2013-2014. Pediatrics. 2017 Jun;139(6):e20163239.
3. Li H-T, Luo S, Trasande L, et al. Geographic variations and temporal trends in cesarean delivery rates in China, 2008-2014. JAMA. 2017 Jan, 3;317(1):69–76.
4. Barash P, Cullen BF, Stoelting RK, Cahalan MK, Stock CM. Clinical anesthesia. Philadelphia: Lippincott Williams & Wilkins; 2009.
5. Pilewska-Kozak AB, Dziurka M, Bałanda-Bałdyga A, et al. Factors conditioning pain control and reduction in post-cesarean section parturients: A cross-sectional study. BMC Pregnancy Childbirth. 2024 May 22;24(1):382.
6. Dahake JS, Verma N, Bawiskar D. Magnesium sulfate and its versatility in anesthesia: A comprehensive review. Cureus. 2024 Mar 17;16(3):e56348.
7. Sane S, Mahdkhah A, Golabi P, Hesami SA, Haki BK. Comparison the effect of bupivacaine plus magnesium sulfate with ropivacaine plus magnesium sulfate infiltration on postoperative pain in patients undergoing lumbar laminectomy with general anesthesia. Br J Neurosurg. 2024 Apr;38(2):256–59.
8. Ma S, Zhang Y, Li Q. Magnesium sulfate reduces postoperative pain in women with cesarean section: A meta-analysis of randomized controlled trials. Pain Pract. 2022 Jan;22(1):8–18.
9. Wang S-C, Pan P-T, Chiu H-Y, Huang C-J. Neuraxial magnesium sulfate improves postoperative analgesia in Cesarean section delivery women: A meta-analysis of randomized controlled trials. Asian J Anesthesiol. 2017 Sep;55(3):56-67.
10. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct;18(343):d5928.
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA, 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021 Mar;29(372):n71.
12. Elsharkawy RA, Farahat TE, Abdelhafez MS. Analgesic effect of adding magnesium sulfate to epidural levobupivacaine in patients with pre-eclampsia undergoing elective cesarean section. J Anaesthesiol Clin Pharmacol. 2018 Jul-Sep;34(3):328–34.
13. Faiz SHR, Rahimzadeh P, Imani F, Bakhtiari A. Intrathecal injection of magnesium sulfate: Shivering prevention during cesarean section: A randomized, double-blinded, controlled study. Korean J Anesthesiol. 2013 Oct;65(4):293–98.
14. Jabalameli M, Pakzadmoghadam SH. Adding different doses of intrathecal magnesium sulfate for spinal anesthesia in the cesarean section: A prospective double blind randomized trial. Adv Biomed Res. 2012;1:7.
15. Malleeswaran S, Panda N, Mathew P, Bagga R. A randomised study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in patients with mild preeclampsia undergoing caesarean section. Int J Obstet Anesth. 2010 Apr;19(2):161–66.
16. Sophia Paleti PKP, Lakshmi BS. A randomized clinical trial of intrathecal magnesium sulfate versus midazolam with epidural administration of 0.75% ropivacaine for patients with preeclampsia scheduled for elective cesarean section. J Anaesthesiol Clin Pharmacol. 2018 Jan-Mar;34(1):23–28.
17. Roopa Sachidananda KB, Shaikh SI, Umesh G, Triveni Bhat BA. Comparison of prophylactic intravenous magnesium sulfate with tramadol for postspinal shivering in elective cesarean section: A placebo controlled randomized double-blind Pilot study. Anesth Essays Res. 2018 Jan-Mar;12(1):130–34.
18. Sun J, Wu X, Xu X, Jin L, Han N, Zhou R. A comparison of epidural magnesium and/or morphine with bupivacaine for postoperative analgesia after cesarean section. Int J Obstet Anesth. 2012 Oct;21(4):310–16.
19. Unlugenc H, Ozalevli M, Gunduz M, Gunasti S, Urunsak IF, Guler T, Isik G. Comparison of intrathecal magnesium, fentanyl, or placebo combined with bupivacaine 0.5% for parturients undergoing elective cesarean delivery. Acta Anaesthesiol Scand. 2009 Mar;53(3):346–53.
20. Xiao F, Xu W, Feng Y, et al. Intrathecal magnesium sulfate does not reduce the ED_{50} of intrathecal hyperbaric bupivacaine for cesarean delivery in healthy parturients: A prospective, double blinded, randomized dose-response trial using the sequential allocation method. BMC Anesthesiol. 2017 Jan 17;17(1):8.
21. Yousef AA, Amr YM. The effect of adding magnesium sulphate to epidural bupivacaine and fentanyl in elective caesarean section using combined spinal-epidural anaesthesia: A prospective double blind randomised study. Int J Obstet Anesth. 2010 Oct;19(4):401–04.
22. Zhong HY, Zhang WP. Effect of intravenous magnesium sulfate on bupivacaine spinal anesthesia in preeclamptic patients. Biomed Pharmacother. 2018 Dec;108:1289–93.
23. Kundra S, Singh RM, Singh G, Singh T, Jarewal V, Katyal S. Efficacy of magnesium sulphate as an adjunct to ropivacaine in local infiltration for postoperative pain following lower segment caesarean section. J Clin And Diagnostic Res. 2016 Apr;10(4):UC18–22.
24. Shah TH, Rubenstein AR, Kosik ES, Heimbach SW, Madamangalam AS. Parturient on magnesium infusion and its effectiveness as an adjuvant analgesic after cesarean delivery: A retrospective analysis. ScientificWorldjournal. 2018 Nov 15;2018:3978760.
25. Hung K-C, Chang L-C, Ho C-N, et al. Influence of intravenous magnesium sulfate infusion on the subjective postoperative quality of recovery: A meta-analysis of randomized controlled trials. Nutrients. 2024 Jul 22;16(14):2375.
26. Kim YA, Kweon TD, Kim M, Lee HI, Lee YJ, Lee K-Y. Comparison of meperidine and nefopam for prevention of shivering during spinal anesthesia. Korean J Anesthesiol. 2013 Mar;64(3):229–33.
27. Berti M, Fanelli G, Casati A, Aldegheri G, Lugani D, Torri G. Hypothermia prevention and treatment. Anaesthesia. 1998;53(2):46–47.
28. Singewald N, Kaehler ST, Hemeida R, Philippu A. Influence of excitatory amino acids on basal and sensory stimuli-induced release of 5-HT in the locus coeruleus. Br J Pharmacol. 1998;123:746–52S.
29. Alojado ME, Ohta Y, Yamamura T, Kemmotsu O. The effect of fentanyl and morphine on neurons in the dorsal raphe nucleus in the rat: An in vitro study. Anesth Analg. 1994;78(4):726–32.
30. Lee C, Zhang X, Kwan WF. Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig. Br J Anaesth. 1996;76:278–83.
31. Low RG, Izaham A, Zain JM, Nor NM, Low HJ, Yusof AM. Prevention of shivering post subarachnoid block: Comparison between different doses of intravenous magnesium sulphate. Medicina (Kaunas). 2022 Aug 3;58(8):1046.
32. Banihashem N, Hasannasab B, Esmaeili A, Hasannasab B. Addition of intrathecal magnesium sulfate to bupivacaine for spinal anesthesia in cesarean section. Anesth Pain Med. 2015 Jun 22;5(3):e22798.
33. Mostafa MF, Herdan R, Fathy GM, et al. Intrathecal dexmedetomidine versus magnesium sulphate for postoperative analgesia and stress response after caesarean delivery; randomized controlled double-blind study. Eur J Pain. 2020 Jan;24(1):182–91.

34. Babaei K, Saadati SM, Samarghandian S, et al. Effects of intrathecal dexmedetomidine vs. magnesium sulfate on post-operative shivering for cesarean delivery: A double-blind randomized clinical trial. Perioper Care Oper Room Manag. 2025 Mar;38:100450.

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