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Review article

Perioperative gabapentin and post cesarean pain control: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Cesarean delivery occurs in roughly one third of pregnancies. Effective postoperative pain control is a goal for patients and physicians. Limiting opioid use in this period is important as some percentage of opioid naïve individuals will develop persistent use. Gabapentin is a non-opioid medication that has been used perioperatively to improve postoperative pain and limit opioid requirements. The goal of this study is to determine the efficacy of perioperative gabapentin in improving post cesarean delivery pain control. The following data sources were searched from their inception through October 2018: MEDLINE, Ovid, ClinicalTrials.gov, Sciencedirect, and the Cochrane Library at the CENTRAL Register of Controlled Trials. A systematic review of the literature was performed to include all randomized trials examining the effect of perioperative gabapentin on post cesarean delivery pain control and other postoperative outcomes. The primary outcome was analgesic effect of gabapentin on post cesarean delivery pain, measured by visual analog scale (VAS; 0–100) or Numerical Rating Scale (NRS; 0–10) on movement 24 h postoperative. These scores were directly compared by multiplying all NRS scores by a factor of 10. Meta-analysis was performed using the random effects model of DerSimonian and Laird, to produce summary treatment effects in terms of mean difference (MD) with 95% confidence interval (CI). Six placebo controlled trials (n = 645) were identified as relevant and included in the meta-analysis. All studies included only healthy pregnant women (American Society of Anesthesiologist (ASA) physical status I or II) undergoing spinal anesthesia for cesarean delivery at term. Participants were randomized to either 600 mg oral gabapentin or placebo preoperatively and in one study the medications were also continued postoperatively. Pooled data showed that women who received gabapentin prior to cesarean delivery had significantly lower VAS pain scores at 24 h after movement (MD -11.58, 95% CI -23.04 to -0.12). VAS pain scores at other time intervals at rest or after movement were not significantly different for those who received gabapentin and placebo although there was a general trend toward lower pain scores for women receiving gabapentin. There was no significant between-group difference in use of additional pain medications, supplemental opioids, and maternal or neonatal side effects. There was higher pain control satisfaction at 12 and 24 h in the gabapentin versus placebo groups.

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Contents

Introduction

Cesarean delivery occurs in approximately 32%, of pregnancies and is one of the most commonly performed surgical procedures in the United States among reproductive aged women [1]. It involves a large abdominal incision, so post-operative pain control is a concern for patients and their families. Poor pain control in the postpartum period has been shown to contribute to postpartum depression and to be a risk factor for developing chronic pain syndromes [2–5].

Regional anesthesia for cesarean delivery typically consists of intrathecal injection of local anesthetic and a lipophilic opioid. The addition of intrathecal morphine has been shown to provide analgesia in the postoperative period for 14–36 h and to reduce postoperative opioid requirements [5]. Regimens for postoperative pain control typically include combinations of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic opioid medications. These may be administered intravenously, intramuscularly, orally, or rectally [3,5].

In addition to optimal postoperative pain control, limiting opioid use is a further goal for healthcare providers as a percentage of opioid naive women will exhibit persistent use postoperatively [6]. As the number of individuals with opioid use disorder continues to rise, alternative analgesic options and strategies to limit opioid consumption become increasingly important.

Gabapentin is an anticonvulsant medication approved by the Federal Drug Administration (FDA) for epilepsy treatment as well as neuropathic pain conditions. It works in part by decreasing excitatory neurotransmitter action in the nervous system to dampen afferent nocioceptive signaling. It has also been used perioperatively for a variety of surgeries to decrease postoperative pain and opioid consumption with varying efficacy. A meta-analysis by Alayed et al. showed reduced postoperative pain scores as well as decreased opioid requirements in the first 24 h following hysterectomy when used perioperatively [7]. Gabapentin is generally considered safe for use in pregnancy, with only rare reports of neonatal withdrawal associated with prolonged use [8].

The aim of this systematic review and meta-analysis was to determine the efficacy of perioperative gabapentin in improving postoperative pain control in healthy women undergoing cesarean delivery at term under spinal anesthesia.

Material and methods

Sources

This review was performed according to a protocol designed a priori and recommended for systematic review [9]. Electronic databases (MEDLINE, Ovid, ClinicalTrials.gov, Sciencedirect, the Cochrane Library at the CENTRAL Register of Controlled Trials) were searched from their inception until October 2018. Search terms used were the following text words: “cesarean,” “caesarean,” “postoperative,” “analgesia,” “pain” and “gabapentin.” No

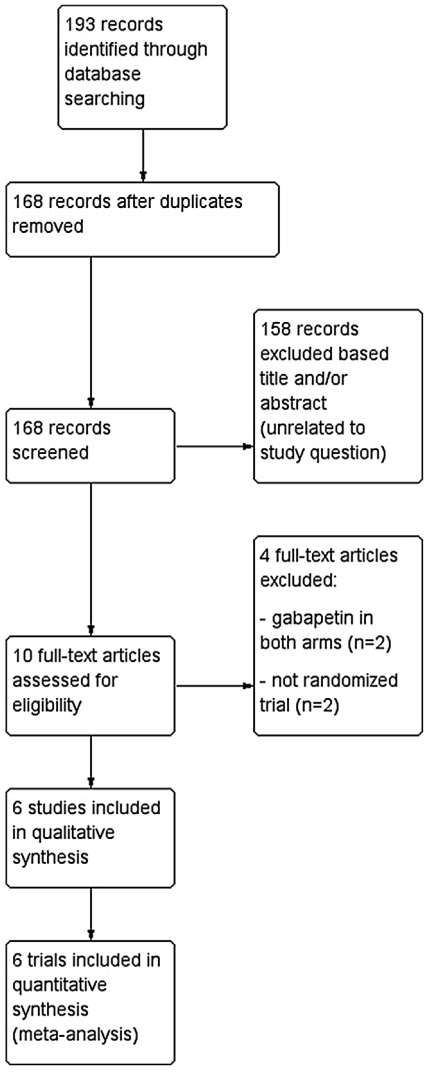

Fig. 1. Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

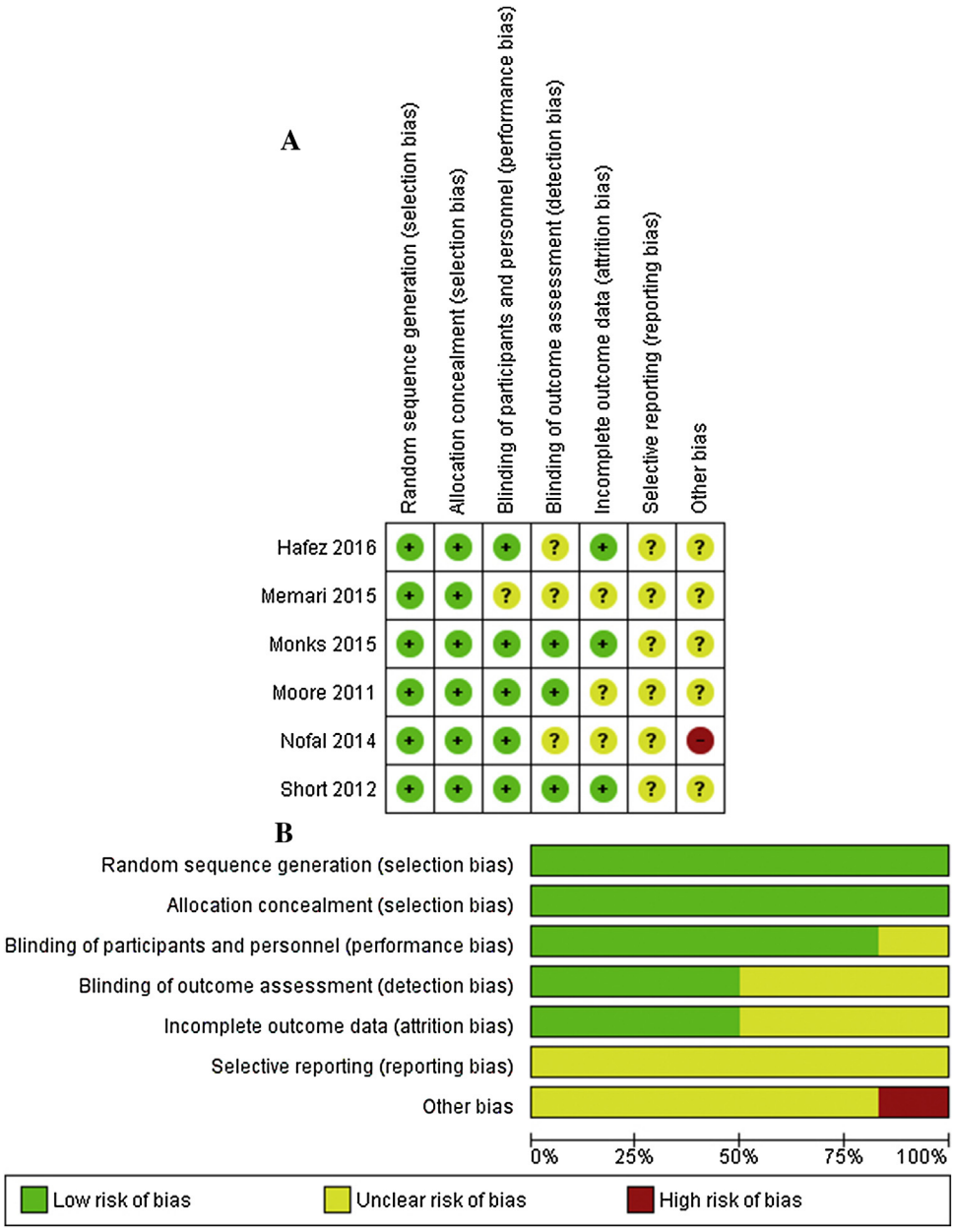

Fig. 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (LF, GS). Differences were discussed and consensus reached.

Study selection

This study included all randomized controlled trials examining the effect of perioperative gabapentin on post cesarean delivery analgesia and other postoperative outcomes including nausea, vomiting, and pain related to spinal headache. Eligible studies included trials comparing patients receiving at least one dose of gabapentin with a control group (either placebo or no treatment).

We included only studies in which women with singleton gestations received spinal anesthesia and underwent cesarean delivery at term (≥37weeks). Trials including multiple gestations, preterm delivery, general anesthesia, studies comparing gabapentin to another drug, and quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation) were excluded.

Risk of bias

The risk of bias in each included study was assessed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random

Table 1
Characteristics of the included trials.

	Study location	Sample size*	Inclusion criteria	Exclusion criteria	Primary outcome
Moore et al. [11]	Canada	44 (21 vs 23)	• Term • Scheduled cesarean • Age ≥18	• HIV • Hepatitis • Uncontrolled HTN or DM • IV drug user • Fetal congenital abnormalities • Use of pain medication in the past week	VAS pain on movement at 24 hrs postop
Short et al. [12]	Canada	88 (44 vs 44)	• Term • Scheduled cesarean • Singleton	• Epilepsy • CNS or mental disorders • Chronic pain • Drug abuse • Use of neuropathic analgesic or antiepileptic drugs • Fetal congenital abnormalities	VAS pain on movement at 24 hours postop
Nofal et al. [13]	Egypt	86 (42 vs 44)	• Term • Scheduled cesarean • Singleton • Primiparous • Multiparous	• Chronic headaches • Chronic pain • Regular analgesics or antiepileptic medication use • Fetal congenital abnormalities	Not reported Post-dural puncture headache characteristics
Memari et al. [14]	Iran	200 (100 vs 100)	• Hemoglobin > 10 g/dl • Fasting 6-8 hours prior to surgery	• Cardiovascular disease • GI disease • Middle ear disease • Vertigo • Motion sickness • DM • HTN • Smoking or alcohol consumption • Nausea/ vomiting before surgery • Fever/ infection • Received additional postoperative medications within 6 hrs (only antibiotics and sedatives)	VAS score for nausea and vomiting postop
Monks et al. [15]	Canada	197 (100 vs 97)	• Term • Scheduled cesarean • Ages 18-55	• Epilepsy • Chronic pain • Use of anticonvulsants or neuropathic analgesics • Opioid or IV drug abuser • Use of antacid in previous 3 hours	VAS pain on movement at 24 h postop
Hafez et al. [16]	Egypt	45 (15 vs 15)	• Term • Scheduled cesarean • 20-40 yrs old • Uncomplicated pregnancy	• Epilepsy • Routine use of antiepileptic medications • Kidney or liver impairment • Alcoholism/ IV drug use • HTN • Oligohydramnios/ polyhydramnios • Antepartum hemorrhage • Psychiatric disorder • Inability to communicate	NRS pain score

HIV: human immunodeficiency virus; HTN: hypertension; DM: diabetes mellitus; CNS: central nervous system; GI: gastrointestinal.
* Data are reported as total number (number in the intervention vs number in the control group).

Table 2
Characteristics of the included women.

	Maternal age	Gestational age at randomization	BMI (kg/m^2)
Moore et al. [11]	35 ± 5 vs 34 ± 6	38.8 ± 0.7 vs 38.9 ± 0.8	29 ± 4 vs 30 ± 6
Short et al. [12]	34.8 ± 4.1 vs 35.3 ± 4.8	38.7 vs 38.5*	30.6 ± 5.6 vs 29.3 ± 4.3
Nofal et al. [13]	32.1 ± 4.8 vs 30.7 ± 5.2	Not reported	Not reported
Memari et al. [14]	26.1 ± 5.2 vs 26.1 ± 5.2	38.2 ± 0.5 vs 38.1 ± 0.4	Not reported
Monks et al. [15]	35.9 ± 3.9 vs 34.7 ± 4.5	38.7 ± 0.8 vs 38.6 ± 0.9	30.8 ± 5.1 vs 31.2 ± 5.6
Hafez et al. [16]	28.2 ± 4.7 vs 27.3 ± 5.5	38.3 ± 1.1 vs 38.1 ± 1.0	Not reported

Data are reported as mean ± standard deviation.
* Median.

Table 3
Preoperative and intraoperative pain management.

	Intervention group	Control group	Timing of intervention	Anesthesia intraoperative medications received by both intervention and control groups	Additional intraoperative meds as needed
Moore et al. [11]	600 mg oral gabapentin	Lactose placebo	1 hr prior to surgery	Intrathecal: 0.75% hyperbaric bupivacaine 12 mg, Fentanyl 10 μg, Morphine100 μg	Up to 100 μg IV fentanyl as needed
Short et al. [12]	600 mg oral gabapentin	Lactose placebo	1 hr prior to surgery	Intrathecal: 13.5 mg 0.75% hyperbaric bupivacaine, 10 μg fentanyl, 100 μg morphine	IV fentanyl at discretion of anesthesiologist
Nofal et al. [13]	600 mg oral gabapentin	Starch placebo	2 hrs prior to surgery	Intrathecal: 12.5 mg hyperbaric bupivacaine 0.5%, 25 μg fentanyl	None
Memari et al. [14]	600 mg oral gabapentin	Placebo	1 hr prior to surgery	Spinal	Not reported
Monks et al. [15]	600 mg oral gabapentin	Placebo	1 hr prior to surgery	Intrathecal: 1.6-1.8 ml 0.75% hyperbaric bupivacaine, 10 μg fentanyl, 100 μg morphine	Up to 100 μg fentanyl IV
Hafez et al. [16]	600 mg oral gabapentin	Placebo	1 hr prior to surgery	Intrathecal: 8 mg bupivacaine, 25 μg fentanyl	None

Hr: hour; IV: intravenous.

Table 4
Intraoperative characteristics.

	Skin incision	Repeated cesarean	Duration of surgery (minutes)
Moore et al. [11]	Not reported	18/21 (85.7%) vs 15/23 (65.2%)	Not reported
Short et al. [12]	Pfannenstiel	30/42 (71.4%) vs 33/42 (78.6%)	Not reported
Nofal et al. [13]	Not reported	26/42 (61.9%) vs 24/44 (54.5%)	55.7 ± 6.9 vs 57.8 ± 7.3
Memari et al. [14]	Not reported	Not reported	Not reported
Monks et al. [15]	Pfannenstiel	76/100 (76.0%) vs 70/97 (72.2%)	Not reported
Hafez et al. [16]	Not reported	Not reported	Not reported

Data are reported as mean ± standard deviation or as number percentage (number in the intervention vs number in the control group).

Table 5
Immediate postoperative medications used in both groups.

	NSAID – immediately postop	Acetaminophen- immediately postop	Postoperative pain meds – standing	Postoperative pain meds – as needed	Anti-emetics, anti-itch
Moore et al. [11]	Ketorolac 30mg IV	Acetaminophen 1g per rectum	• Diclofenac 50mg q8h po • Acetaminophen 1 g po q6h for 72 hrs	• PACU: Morphine 2 mg IV q5 mins prn • Ward: Morphine 2mg subcutaneous q4hrs in first 24 hrs, then 5 mg po q4 hrs	• Dimenhydrinate 50 IM q6h • Diphenhydramine 25 IM q4h
Short et al. [12]	Ketorolac 30 mg IV	Acetaminophen 1300mg per rectum	• Diclofenac 50mg q8h po • Acetaminophen 1 g q6h po x 72 hrs	• First 24 hrs: Morphine 2 mg subcutaneous prn • After: Morphine 10 mg po	• Dimenhydrinate 50 mg IM q6h prn • Nalbuphine 5 mg subcutaneous q4h prn
Nofal et al. [13]	Not reported	Not reported	• Diclofenac 50mg IM alternating with IV Acetaminophen q 12 hours	• Meperidine 50 mg IM prn	All received antacids
Memari et al. [14]	Not reported	Not reported	Not reported	Not reported	Not reported
Monks et al. [15]	Ketorolac 30 mg IV	Acetaminophen 1300 mg per rectum	• Diclofenac 50mg q8h • Acetaminophen 1g po q6h • Gabapentin 200mg or placebo q8 x 48 hrs	• PACU: Morphine 2mg IVq5mins • Floor: • First 24h: Morphine subcutaneous or IV 2mg or Hydromorphone 0.4mg q1h • After 24h: Morphine 10mg po or Hydromorphone 2 mg	• Zofran • Metoclopramide • Dimenhydrinate
Hafez et al. [16]	Not reported	Not reported	Not Reported	• Meperidine IV 1 mg/kg IM in first 24 hrs	• Zofran • Ranitidine

IV: intravenous; po: per os (oral); IM: intramuscular; q: every; h: hours; prn: pro re nata (as needed).

sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias [9].

Two authors (LF, GS) independently assessed inclusion criteria, risk of bias and data extraction. Disagreements were resolved by discussion.

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they

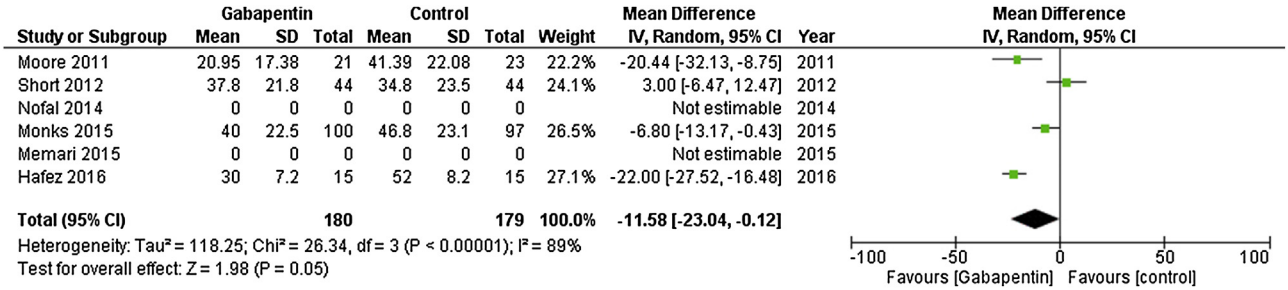

Fig. 3. Forest plot for the risk of VAS pain scores at postoperative on movement.

Table 6
VAS Pain scores outcomes.

	VAS 6 h movement (mm)	VAS 6 h rest (mm)	VAS 12h Movement (mm)	VAS 12h Rest (mm)	VAS 24 h movement (mm)	VAS 24 h rest (mm)	VAS 48 h movement (mm)	VAS 48 h rest (mm)
Moore et al. [11]	Not Reported	Not Reported	19.95 ± 16.87 vs 45.00 ± 24.39	11.86 ± 10.36 vs 22.61 ± 20.23	20.95 ± 17.38 vs 41.39 ± 22.08	12.05 ± 13.88 vs 18.70 ± 15.53	17.29 ± 17.96 vs 32.09 ± 21.67	7.9 ± 11.94 vs 14.41 ± 17.91
Short et al. [12]	31.5 ± 23.3 vs 39.5 ± 26.9	15.3 ± 15.1 vs 19.3 ± 20.9	32.7 ± 22.5 vs 38.7 ± 23.6	15.6 ± 14.9 vs 16.7 ± 15.9	37.8 ± 21.8 vs 34.8 ± 23.5	15.3 ± 16.0 vs 14.3 ± 15.6	26.5 ± 19.2 vs 34.3 ± 24.1	13.2 ± 12.8 vs 13.7 ± 16.9
Nofal et al. [13]	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported
Memari et al. [14]	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported
Monks et al. [15]	Not Reported	Not Reported	Not Reported	Not Reported	40.0 ± 22.5 vs 46.8 ± 23.1	13.1 ± 16.7 vs 19.1 ± 18.1	34.0 ± 21.5 vs 36.0 ± 24.5	13.0 ± 15.3 vs 16.0 ± 17.0
Hafez et al. [16]	42.0 ±-8.1 vs 29.0 ± 9.0	Not Reported	30.0 ± 8.0 vs 23.0 ± 16.0	Not Reported	30.0 ± 7.2 vs 52.0 ± 8.2	Not Reported	Not Reported	Not Reported
Total	36.8 vs 34.3	15.3 vs 19.3	27.5 vs 35.6	13.7 vs 19.7	32.2 vs 43.7	13.5 vs 17.4	25.9 vs 34.1	11.4 vs 14.7
I^2	91%	N/A	88%	64%	89%	38%	47%	0%
MD (95% CI)	2.99 (−17.57 to 23.54)	−4.00 (−11.80 to 3.80)	−7.60 (−24.97 to 9.77)	−5.32 (−14.71 to 4.06)	**−11.60 (−23.03 to -0.16)**	−3.90 (−8.62 to 0.82)	−6.90 (−13.92 to 0.13)	−3.03 (−6.45 to 0.38)

Data are reported as mean ± standard deviation in the intervention vs control group.
MD, mean difference; CI, confidence interval; N/A, not applicable.

were randomly allocated in the original trials. This review was registered with the PROSPERO International Prospective Register of Systematic Reviews (Registration Number: CRD42018099832).

Primary and secondary outcomes

The primary outcome was the VAS pain score on movement at 24 h postoperative. Secondary outcomes were VAS pain scores at other time intervals both at rest or on movement following surgery, use of additional intraoperative pain medications or supplemental opioids, pain control satisfaction, persistent pain after cesarean delivery, maternal side effects, and neonatal outcomes. Maternal side effects examined include nausea, vomiting, pruritus, and sedation. Neonatal outcomes evaluated include APGARs at 1 and 5 min, birth weight, umbilical cord arterial pH, neonatal intensive care unit admissions, breast feeding difficulties in first 24 h, and need for positive pressure ventilation.

Statistical analysis

The data analysis was completed independently by two authors (LF, GS) using Review Manager v. 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved by discussion with a third reviewer (VB).

Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. A 2 by 2 table was assessed for relative risk (RR); for continuous outcomes, means ± standard deviation were extracted and imported into Review Manager v. 5.3.

Meta-analysis was performed using the random effects model of DerSimonian and Laird, to produce summary treatment effects in terms of either a RR or mean difference (MD) with 95% confidence interval (CI). Heterogeneity was measured using I-squared (Higgins I^2).

Potential publication biases were assessed statistically using Begg's and Egger's tests. P value <0.05 was considered statistically significant.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [10].

Results

Study selection and study characteristics

The flow of study identification is shown in Fig. 1. Six trials were identified as relevant, included in the meta-analysis and analyzed [11–16]. Publication bias, assessed statistically using Begg's and Egger's test, showed no significant bias (P = 0.57 and P = 0.52, respectively). Statistical heterogeneity within the trials ranged from low to moderate with no inconsistency (I^2 = 0%) for several of the secondary outcomes, and I^2 = 89% for the primary outcome.

The quality of the RCTs included in our meta-analysis was assessed using the seven criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Most of the included studies were judged as "low risk" of bias in most of the seven Cochrane domains related to the risk of bias. All the included studies had "low risk" of bias in "random sequence generation." All the trials were placebo-controlled studies, and neither the

Table 7
Secondary outcomes.

	Women requiring additional intraoperative pain medications	Average mg of IV morphine equivalents used as needed in 24 hours for patients requiring additional analgesia	Women requiring supplemental narcotics in first 24 hrs	Pain control satisfaction 6 hrs (mm)	Pain control satisfaction 12 hrs (mm)	Pain control satisfaction 24 hrs (mm)	Pain control satisfaction 48 hrs (mm)	Persistent pain 6 weeks after delivery
Moore et al. [11]	0/21 vs 1/23 (4.3%)	4.2 ± 2.5 vs 3.2 ± 1.8	5/21 (23.8%) vs 5/23 (21.7%)	Not reported	94.8 ± 8.1 vs 79.1 ± 20.0	90. ±15.5 vs 77.8 ± 17.8	92.9 ± 11.0 vs 87.3 ± 12.4	2/16 (12.5%) vs 4/20 (20.0%)
Short et al. [12]	1/42 (2.4%) vs 3/42 (7.1%)	6.7 ± 3.6 vs 7.9 ± 3.8	14/42 (33.3%) vs 16/42 (30.1%)	84.0 ± 20.0 vs 82.0 ± 21.0	84.7 ± 17.7 vs 78.2 ± 22.6	85.3 ± 15.1 vs 80.5 ± 21.6	81.0 ± 24.0 vs 83.8 ± 18.5	6/42 (14.3%) vs 1/42 (2.4%)
Nofal et al. [13]	0/42 vs 0/44	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Memari et al. [14]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Monks et al. [15]	1/100 (1.0%) vs 3/97 (3.1%)	8.7 ± 5.2 vs 9.1 ± 6.7	23/100 (23) vs 31/97 (32)	Not reported	Not reported	86.5 ± 17.5 vs 77 ± 22.9	85.5 ± 19.3 vs 81.3 ± 21.4	4/71(5.6%) vs 3/71 (4.2%)
Hafez et al. [16]	0/15 vs 0/15	Not reported	15/15 (100%) vs 15/15 (100%)	Not reported	Not reported	Not reported	Not reported	Not reported
Total	2/205 (1.0%) vs 7/206 (3.4%)	6.5 vs 6.7	57/178 (32.0%) vs 67/177 (37.9%)	84.0 vs 82.0	89.8 vs 78.7	87.3 vs 78.4	–	12/129 (9.3%) vs 8/133 (6.0%)
I [2]	0%	58%	60%	Not applicable	54%	0%	13%	34%
RR or MD (95% CI)	0.32 (0.08 to 1.38)	−0.14 (-1.48 to 1.20)	0.90 (0.62 to 1.29)	2.00 (−6.57 to 10.57)	**11.00 (1.99 to 20.02)**	**8.64 (4.47 to 12.81)**	3.20 (−1.09 to 7.48)	1.47 (0.45 to 4.79)

Data are reported as mean ± standard deviation or as number (percentage) in the intervention vs control group. Boldface data, statistically significant.
MD, mean difference; CI, confidence interval; RR, relative risk.

Table 8
Maternal Side effects within 48 h.

	Nausea	Vomiting	Pruritus	Sedation
Moore et al. [11]	12/21 (57.1%) vs 8/23 (34.8%)	5/21 (23.8%) vs 3/23 (13.0%)	16/21 (76.2%) vs 22/23 (95.7%)	17/21 (80.9%) vs 17/23 (73.9)
Short et al. [12]	19/42 (45.2%) vs 19/42 (45.2%)	7/42 (16.7%) vs 10/42 (23.8%)	33/42 (78.6%) vs 32/42 (80.9%)	23/42 (54.8%) vs 24/42 (57.1%)
Nofal et al. [13]	7/42 (16.6%) vs 9/44 (20.5%)	Not reported	Not reported	11/42 (26.2%) vs 3/44 (6.8%)
Memari et al. [14]	27/100 (27.0%) vs 41/100 (41.0%)	25/100 (25.0%) vs 38/100 (38.0%)	Not reported	Not reported
Monks et al. [15]	38/100 (38.0%) vs 42/97 (43.3%)	24/100 (26.0%) vs 26/97 (26.8%)	72/100 (72.0%) vs 77/97 (79.4%)	55/100 (55.0%) vs 38/97 (39.2%)
Hafez et al. [16]	Not reported	Not reported	Not reported	Not reported
Total	103/305 (33.8%) vs 119/309 (38.5%)	61/263 (23.2%) vs 77/262 (29.4%)	121/163 (74.2%) vs 131/162 (80.9%)	106/205 (51.7%) vs 82/206 (39.8%)
I [2]	30%	0%	9%	57%
RR (95% CI)	0.90 (0.69 to 1.17)	0.78 (0.58 to 1.04)	0.91 (0.81 to 1.03)	1.24 (0.90 to 1.69)

Data are reported as number in the intervention vs number in the control group.
RR, relative risk; CI, confidence interval.

Table 9
Neonatal Outcomes.

	1 min APGAR (median)	5 min APGAR (median)	Umbilical cord arterial pH	NICU admission	Breast feeding difficulties first 24 hrs	Birth weight (grams)	Positive Pressure Ventilation
Moore et al. [11]	9 vs 9	9 vs 9	7.3 ± 0.1 vs 7.3 ± 0.1	1/21 (4.76%) vs 0/23 (0)	3/20 (15%) vs 5/21 (23.81%)	3520 ± 407 vs 3341 ± 431	Not reported
Short et al. [12]	9 vs 9	9 vs 9	7.3 ± 0.1 vs 7.3 ± 0.1	1/42 (2.4%) 2/42 (4.8%)	1/42 (2.4%) vs 7/42 (16.7%)	3505 ± 431 vs 3382 ±553	2/42 (4.76%) vs 2/42 (4.76%)
Nofal et al. [13]	9 vs 9	9 vs 9	7.3 ± 0.1 vs 7.3 ± 0.1	2/42 vs 1/44	2/42 vs 1/44	3,251 ± 522 vs 3,347 ± 581	Not reported
Memari et al. [14]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Monks et al. [15]	9 vs 9	9 vs 9	7.3 ± 0.1 vs 7.3 ± 0.1	1/100 (1) vs 4/97 (4.1)	16/91 (17.6) vs 17/88 (19.3)	3408 ± 449.7 vs 3,347 ± 5.5.5	3/100 (3) vs 3/97 (3.1)
Hafez et al. [16]	9 vs 9	10 vs 10	Not reported	Not reported	Not reported	Not reported	Not reported
Total	–	–	7.3 vs 7.3	5/205 (2.4%) vs 7/206 (3.4%)	22/195 (11.3%) vs 30/195 (15/4%)	3407.2 vs 3353.5	5/142 (3.5%) vs 5/139 (3.6%)
I^2	–	–	22%	0%	20%	0%	0%
RR or MD (95% CI)	–	–	−0.01 (−0.02 to 0.00)	0.77 (0.23 to 2.62)	0.74 (0.37 to 1.48)	65.46 (−30.73 to 161.66)	0.98 (0.29 to 3.31)

Data are reported as number in the intervention vs number in the control group.
MD, mean difference; CI, confidence interval; RR, relative risk.

participants nor the investigators were aware of the treatment assignments (Fig. 2).

All six trials included only healthy pregnant women with singleton gestations undergoing cesarean delivery at term under regional anesthesia. Healthy was defined as ASA I or II, which includes pregnant women with BMI less than 40 mg/kg, with no medical problems or well controlled diabetes/hypertension, or mild lung disease. There were a total of 320 women in the intervention group and 321 women in the control group. VAS pain score was the most used primary outcome, assessed in four of six trials and a total of 178 women in the intervention group and 177 women in the control group had available data for this outcome (Table 1). The mean gestational age at randomization was about 38 weeks in both groups (Table 2). All trials used 600 mg oral gabapentin as intervention, and placebo as control, 1 h (in 5/6 trials) before surgery and in one study gabapentin was continued postoperatively for 48 h (Table 3). Both gabapentin and placebo groups received the same intrathecal opioids in each study (Table 3). Only four trials reported on repeat cesarean (the majority of women), and only two on type of skin incision (Pfannenstiel) (Table 4). Immediate postoperative medications used in both groups– an NSAID, usually ketorolac or diclofenac, as well as acetaminophen - are reported in Table 5.

Synthesis of results

Women who received 600 mg oral gabapentin prior to cesarean delivery, had lower VAS pain scores at 24 h postoperative on movement compared to those who received placebo (36.4 vs 43.7, MD -11.60, 95% CI-23.03 to -0.16; Fig. 3) (Table 6). VAS pain scores at 6, 12, 24, and 48 h at rest or after movement were not statistically different for women receiving gabapentin and placebo although there was a general trend towards lower VAS pain scores for women receiving gabapentin (Table 6). There was no significant between-group difference in use of additional pain medications, supplemental opioids, and persistent pain 6 weeks after cesarean delivery (Table 7). There was a higher pain control satisfaction at 12 and 24 h in the gabapentin vs placebo groups (Table 7). There were no significant between-group differences in maternal side effects of nausea, vomiting, pruritus, or sedation (Table 8). No data were reported in any study regarding headache, hypotension, and shivering which were included in the initial study design. Neonatal outcomes were similar in the two groups with respect to 1 and 5 min APGARs, birth weight, NICU admission, umbilical cord arterial pH, breast feeding difficulties in first 24 h, and need for positive pressure ventilation (Table 9).

Discussion

In healthy term pregnant women undergoing cesarean delivery under spinal anesthesia with intrathecal opioids, as well as standing NSAIDs and acetaminophen postpartum, 600 mg oral gabapentin 1 h before surgery was associated with lower VAS pain scores in the postoperative period compared to those who received placebo, reaching statistical significance at 24 h on movement. There is also a significant difference in VAS pain score satisfaction at 12 and 24 h although this finding is limited by having data from only 2 and 3 studies respectively.

There is conflicting data regarding the efficacy of perioperative gabapentin to decrease postoperative pain. In non-pregnant adults, some meta-analyses have failed to show an improvement in postoperative pain scores or opioid use following perioperative gabapentin administration while others have demonstrated statistically significant improvements in these outcomes when perioperative gabapentin is used [17–21]. A meta-analysis by Alayed et al showed decreasing postoperative opioid requirements, as well as lower VAS pain scores in the first 24 h following total abdominal hysterectomy when 400 to 1800 mg gabapentin was dosed perioperatively [7]. Importantly, this study included only patients undergoing general anesthesia in contrast to our study, which includes only patients receiving regional anesthesia with intrathecal opioids where a postoperative analgesic effect is expected for up to 36 h [5]. A meta-analysis by Doleman et al included studies where patients received both general and spinal anesthesia and showed a lesser effect on pain medication requirements for patients that underwent spinal anesthesia compared to general anesthesia when receiving preoperative gabapentin [20]. In other words, preoperative gabapentin was more effective in decreasing postoperative opioid consumption in patients receiving general anesthesia compared to regional anesthesia.

Strengths of this meta-analysis include the methodology used to conduct the analysis which followed criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. All authors were contacted directly and additional unpublished data was compiled for analysis. Additionally, the included studies had low risk of bias.

This study is limited by characteristics inherent to the individual studies included for analysis. Only four of the included six studies assessed the primary outcome of VAS pain scores. Two of four studies showed a decrease in postoperative VAS pain scores and narcotic usage following pre-cesarean gabapentin administration compared to placebo, while two showed no difference. Of these four studies, three were adequately powered to detect such a difference and one that failed to show an intervention effect was not. Neuraxial medications and intraoperative/ postoperative analgesic medications as well as dose and route varied between studies but were overall similar. Women in all studies where neuraxial medications are reported (5/6) received intrathecal bupivacaine and fentanyl and in 3/5 studies women also received intrathecal morphine. This study is also limited in generalizability as all patients were healthy with ASA class I or II and patients with substance use disorders or chronic pain syndromes were excluded. Data regarding intraoperative surgical technique were not reported and different techniques have been associated with varying painfulness [2,22–24]. Original trials did not reported on duration of surgery, or on abdominal adhesions.

An optimal approach to post partum pain control remains incompletely characterized. Different approaches have been studied, including antenatal and postnatal interventions [25–29]. Limiting opioid usage in this period is a priority as data have shown that 1 in 300 opioid naïve individuals will continue to use opioids after the postoperative period [6]. Current anesthesia guidelines recommend a multi-modal, step-wise approach that is individualized to each patient. Women receiving regional anesthesia with intrathecal morphine should receive NSAIDs and acetaminophen with additional opioids reserved for "severe breakthrough pain" [5]. While this meta-analysis is limited by a small number of patients, it does support a role for prophylactic gabapentin in reducing postoperative VAS pain scores after cesarean delivery. Importantly, no difference was seen in maternal side effects or neonatal outcomes for patients receiving preoperative gabapentin highlighting its safety for use in this patient population.

Conclusions

In summary, prophylactic use of 600 mg oral gabapentin prior to cesarean delivery improves postoperative pain control in healthy patients (ASA I or II) undergoing spinal anesthesia with intrathecal opioids, as well as receiving standing NSAIDs and acetaminophen postpartum.

Disclosure

The authors report no conflict of interest.

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