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Systemic Reviews

A systematic review and network meta-analysis of the use of gabapentinoids perioperatively at the time of cesarean for reducing opioid use.

Hani Faysal, M.D.[1], David Haas, M.D., M.S[1], Kemi Ogunmuko, M.D.[1], Joanne Daggy, PhD.[2], Elizabeth Whipple, MLS.[3]

[1] Obstetrics and Gynecology, Indiana University School of Medicine, [2] Biostatistics and Health Data Science, Indiana University School of Medicine, [3] Ruth Lilly Medical Library, Indiana University School of Medicine

Keywords: cesarean, gabapentin, pregabalin, pain, opioids, systematic review/meta-analysis, enhanced recovery after surgery, perioperative, maternal morbidity, morphine milligram equivalent

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Background

Cesarean section (CS) is the world's most common major surgical procedure. Subsequently, inadequate pain control contributes to post-partum depression, impaired bonding with infants, and is a risk factor for developing chronic pain syndromes. In light of this, there has been an increased interest in using gabapentin as part of pain-reducing strategies for patients undergoing CS.

Objectives

To systematically review and synthesize published data regarding the use of gabapentinoids as adjuncts to cesarean section (CS) pain control on opioid consumption, pain scores, and patient satisfaction.

Study Design

We searched Ovid MEDLINE, Ovid Embase, and Cochrane. The literature search was run on May 6th, 2024, around the main concepts for "Cesarean Section," "Gabapentin," and "Pregabalin" and adapted for each database as necessary, from their inception until May 2024. Study eligibility criteria were randomized controlled trials (RCTs) and observational studies that used gabapentin or pregabalin pre- and/or postoperatively at the time of CS. Studies were excluded if there was no comparison group that did not receive either of the drugs. Two reviewers evaluated all studies for eligibility, assessed risk of bias using standard tools, and extracted data for analysis. Network meta-analysis was performed using the random effects model approach due to the inclusion of multi-arm studies and the heterogeneity of studies.

Results

11 studies (9 RCTs, 2 observational studies) were included, with generally low risk of bias. Only the observational studies used gabapentin as part of an enhanced recovery after CS protocol. A total of 597 participants received gabapentin or pregabalin and 498 were controls. When including all study designs, one pre-operative 600mg dose of gabapentin decreased post-CS opioid use (measured with milligram morphine equivalents (MME), -20.72, 95% confidence interval (CI) [-33.52, -7.23]). When limiting the analysis to RCTs, a single 300mg dose of either gabapentin or pregabalin reduced MMEs (-4.30, 95% CI [-8.25, -0.36]; -6.90, 95% CI [-8.51, -5.29], respectively). Pain scores were also lower with 600mg and 900mg doses of gabapentin (-1.01, 95% CI [-1.98, -0.04] and -2.50, 95% CI [-4.28, -0.71], respectively). Four studies reported patient satisfaction, with only the 300mg gabapentin dose improving satisfaction scores compared to placebo (mean difference: 1.35, 95% CI [0.45, 2.24]).

Conclusions

Limited evidence demonstrates that including gabapentin or pregabalin to programs of pain management for CS may decrease total MME requirements, decrease pain, and improve satisfaction.

INTRODUCTION

Cesarean section (CS) is the world's most common major surgical procedure (Pfuntner, W. L. M., and Stocks 2013). It accounts for approximately 32% of births in the United States and is predicted to trend upward through 2030 (Betran et al. 2021; Martin et al. 2015). CS involves a large abdominal incision, making the effective delivery of postoperative analgesia of primary importance. Indeed, patients rank perioperative avoidance of pain as their highest priority regarding anesthesia outcomes (Carvalho et al. 2005). Inadequate pain control contributes to post-partum depression, impaired bonding with infants, and is a risk factor for developing chronic pain syndromes (Eisenach et al. 2008; Apfelbaum et al. 2016; Toledo, Miller, and Wisner 2018; Sutton and Carvalho 2017).

Regional anesthesia for CS, consisting typically of an intrathecal injection of a local anesthetic in addition to a lipophilic opioid, provides analgesia post-operatively for up to 36 hours while also reducing post-operative opioid requirements (Sutton and Carvalho 2017). However, many opioid naïve patients will require persistent opioid use postoperatively (Bateman et al. 2016). Considering the rising number of individuals with opioid use disorder, alternative analgesic agents and strategies have been explored to limit opioid consumption after CS (Lyden and Binswanger 2019).

Gabapentin is an anticonvulsant medication first discovered in the 1970, receiving FDA approval in 1993 for use in the United States (Lumsden et al. 2019). Initially used as a muscle relaxer and an anti-spasmodic, it has now been approved by the FDA for multiple conditions such as epilepsy and neuropathic pain conditions (Yasaei, Katta, and Saadabadi 2022; Felder et al. 2019a). It works by binding voltage-gated calcium channels inhibiting the release of excitatory neurotransmitters (Yasaei, Katta, and Saadabadi 2022). Gabapentin has been used as preemptive analgesia or as a supplement for postoperative (i.e. abdominal and vaginal hysterectomies) analgesia, resulting in decreased opioid-associated vomiting and pruritus (Ho, Gan, and Habib 2006). Gabapentin also demonstrated reduction in postoperative pain scores and opioid requirements 24 hours following hysterectomy when administered perioperatively (Alayed et al. 2014). There has been an increased interest in using gabapentin as part of pain-reducing strategies for patients undergoing CS.

The objective of this study, a systematic review (SR), was to characterize perioperative gabapentin use and outcomes in patients undergoing CS. The related goal of this study was to determine if using gabapentin in the perioperative timeframe reduced opioid requirements and postoperative pain in patients undergoing a CS.

MATERIALS AND METHODS

We conducted a systematic review of the literature for studies utilizing gabapentin as part of the perioperative pain management strategy for patients undergoing a CD. This is a PROSPERO trial (ID: CRD42024538992), submitted on April 22nd, 2024, and registered on May 5th, 2024.

The search strategy was composed and conducted by a medical librarian in Ovid MEDLINE, Ovid Embase, and Cochrane. The final literature search was run on May 6th, 2024, around the main concepts for "Cesarean Section," "Gabapentin," and "Pregabalin" and adapted for each database as necessary, from their inception until May 2024. The search strategy for Ovid MEDLINE included: ("Cesarean Section" OR "Cesarea*" OR "Caesarea*" OR "c section*" OR "abdominal deliver*" OR "ex utero intrapartum treatment procedure*") AND ("Gabapentin" OR "Pregabalin" OR "gabapentin*" OR "Neurontin*" OR "pregabalin*" OR "ci1008*" OR "ci 1008" OR "Lyrica*"). Additional reference lists of identified original articles or reviews were searched manually. Randomized controlled trials (RCTs) and observational studies were included. No restrictions regarding parity, age, ethnicity, maternal comorbidities, or indication for CS were applied. Studies were included if they used gabapentin or pregabalin pre- and/or postoperatively at the time of CS. Studies were excluded if there was no comparison group in which a placebo or intervention other than gabapentinoids was given. Observational studies were included if it was clear which participants received the gabapentin or pregabalin and which did not.

Retrieved articles were assessed independently by two reviewers (HF and KO) to verify their eligibility. Any discrepancies in reviewers' opinions on inclusion or exclusion of any article were discussed with a third reviewer (DH) to reach a consensus. Titles and abstracts were initially assessed and ones that appeared relevant had full text manuscripts retrieved, when possible, for full evaluation.

A search of PROSPERO May 2024 using the terms "gabapentin" and "cesarean" revealed no hits for other systematic reviews on the site.

Data extraction was focused on design (authors, study design), participants (number of participants in intervention and control groups), interventions (different regimens, frequency, timing, control type, con-interventions, analgesics used during CS), and outcomes (Mixed Morphine Equivalents (MME), Pain Scores (VAS, NRS, or POD), Patient satisfaction). Data from studies was also extracted by 2 of the authors and any discrepancies resolved by consensus.

We conducted risk of bias assessments using the Cochrane tools for randomized control trials (RoB-2 tool) (Sterne et al. 2019), the Risk of Bias Assessment tool for non-randomized studies of Interventions (ROBINS-I) tool for the observational studies (Sterne et al. 2016), and re-

ported it according to the PRISMA Statement 2020 (Page et al. 2021).

Two reviewers (HF and KO) independently assessed the risk of bias in each study using the Risk of Bias Assessment tool for non-randomized studies of Interventions (ROBINS-I) tool for the observational studies (Sterne et al. 2016). RoB 2 tool was used to assess the risk of bias of the RCTs (Sterne et al. 2019). Any discrepancies were resolved by a third author (DH).

Summary descriptive information from each included study were extracted. The primary outcome was total cumulative opioid pain medication required after cesarean as morphine milligram equivalents (MME), typically measured during the first 48 hours of the hospital stay. Secondary outcomes included maximal pain scores measured with movement at 24 hours after the procedure (NRS pain scores), and participant satisfaction with pain. Outcomes of pain at activity at 24 hours was estimated from the VAS, NRS, or POD found in the articles, by converting all to the NRS (Supplemental material). Similarly, satisfaction with pain was measured on different scales and converted to 0 to 10. Appropriate statistical methods were used to convert different summary statistics provided to the mean and standard deviations for use in the network meta-analysis (Hozo, Djulbegovic, and Hozo 2005; Wan et al. 2014; Cai, Zhou, and Pan 2021). Only descriptive statistics were provided for adverse events due to the heterogeneity in assessment.

A network meta-analysis (NMA) was conducted for each outcome using a frequentist approach which adjusts for the correlation between multiple comparisons within multi-arm studies (Franchini et al. 2012; Rücker and Schwarzer 2014). Analysis was conducted with the netmeta package in R software (Balduzzi et al. 2023). Network meta-analysis allows us to incorporate the most evidence and can provide direct and indirect evidence on contrasts of interest such as pairwise difference between two means. Mean differences in outcomes and associated 95% confidence intervals are reported in league tables. For each outcome, a random effects NMA was fit including all studies and also for the subset of randomized controlled trials only. Random effects models were conducted due to the heterogeneity in studies and populations.

RESULTS

The study selection process is described in Figure 1. Our initial search yielded 726 titles, of which 18 were deemed relevant and full texts requested. We included 13 studies in the final analysis, 10 RCTs and 3 observational studies (Moore et al. 2011; Short et al. 2011; Nofal, Mahmoud, and Al Alim 2014; Memari et al. 2015; Monks et al. 2015; Hafez et al. 2017; Randolf et al. 2019; Najafi Anaraki and Mirzaei 2014; Karami, Hoshyar, and Jafari 2021; El Kenany and El Tahan 2016; Grasch et al. 2023; MacGregor et al. 2021; Ende et al. 2022). Risk of bias was reported to be overall low in both observational studies and randomized control trials, except for the Memari study that had some concerns in biases arising from randomization and outcome measurement (fig.2-3) (Memari et al. 2015). All the RCTs were placebo-controlled studies with blinding of investigators and participants, with an exception in the Anaraki trial that used intrathecal fentanyl in the control group as opposed to pre-operative oral gabapentin (table 1) (Najafi Anaraki and Mirzaei 2014). Most trials included healthy pregnant patients with a singleton gestation, undergoing scheduled cesarean delivery at term. Study location, sample sizes, inclusion and exclusion criteria are described in Table 1.

A total of 597 patients were in the intervention groups and 498 in the control group. VAS pain on movement at 24 hours post-op was the most reported outcome (n=7), followed by MMEs and NRS pain scores (Table 1). Five studies reported patient satisfaction outcomes. Two observational studies incorporated gabapentin as part of CS enhanced recovery protocols (ERAS). Both observational studies noted benefits. Seven of the eight trials using only preoperative gabapentin showed some benefit. The typical mean gestational age at randomization was about 38 weeks. The maternal age, gestational age, and BMI describing the patient populations are found in Table 2. Administered doses of gabapentin ranged from 200mg to 900mg, and from 150-300mg for pregabalin. Timing of doses was up to 1 hour pre-op for most studies, except for two studies where gabapentin was continued post-operatively for 48 hours (Grasch et al. 2023; MacGregor et al. 2021).

From a random effects NMA model, treatment with 600 mg of gabapentin preoperatively, compared to no treatment or placebo, was associated with a decrease in cumulative opioid requirements post-operatively in MME (-20.72, 95% [CI -33.52, -7.93]) when including all study designs (Figure 4). When limiting the analysis to randomized trials, treatment with 300 mg of gabapentin or pregabalin preoperatively also led to reduced opioid use (MME: -4.30, 95% CI [-8.25, -0.36]; -6.90, 95% CI [-8.51, -5.29], respectively) (Figure 5, Table 3). Using the same model for RCT studies only for the outcome of pain, 600 mg and 900 mg of gabapentin were associated with lower pain scores (-1.01, 95% CI [-1.98, -0.04] and -2.50, 95% CI [-4.28, -0.71], respectively) (Figure 6, Table 4). Results are similar when including all study designs for pain on movement (Supplemental Figure 1). From the limited studies that report satisfaction (n= 4; all using gabapentin), satisfaction was higher for those in treatment groups (200 mg/both, 300 mg, and 600 mg), but only the 300 mg dose of gabapentin provided significantly higher satisfaction (1.35, 95% CI [0.45, 2.24]) than the control group (Figure 7).

DISCUSSION

PRINCIPAL FINDINGS

Administration of 300-600mg of gabapentin and 300mg of pregabalin led to a significant decrease in MMEs in term-pregnant patients undergoing CS. Even small reductions in opioid requirements after CS can be important for patient recovery. Regarding pain scores, 600-900mg of gabapentin led to lower scores overall. Additionally, 300mg of

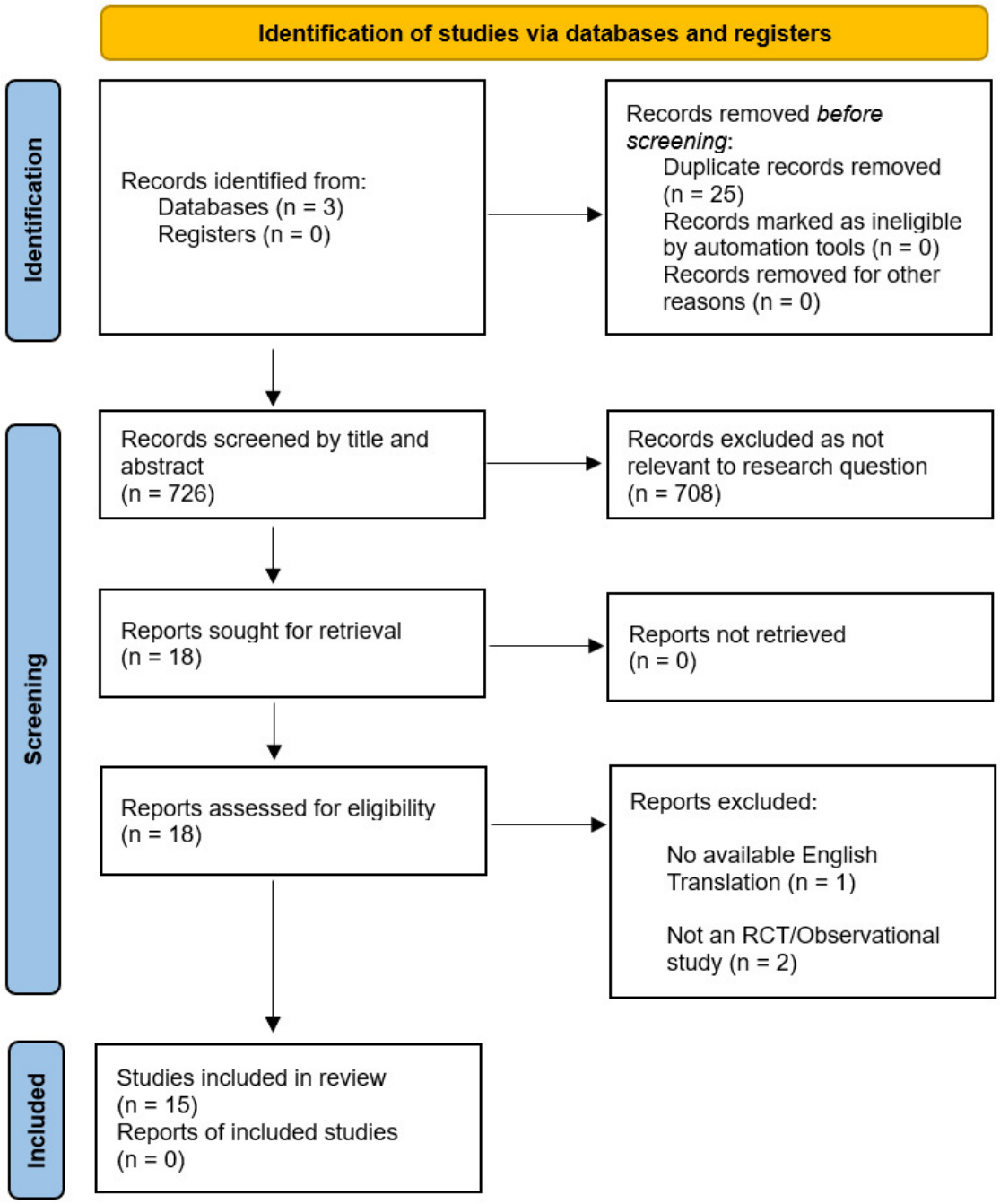

Figure 1. PRISMA 2020 flow diagram depicting study identification process.

gabapentin drove satisfaction with pain control scores significantly higher.

RESULTS

The findings demonstrated are in accordance with the results of a previous SR-MA by Felder et. al. evaluating the relation between perioperative gabapentin and post-CS pain control (Felder et al. 2019b). This study differs from the Felder SR-MA due to the inclusion of 5 additional studies, 3 RCTs (Karami, El Kenany, and Anaraki), and 2 observational (MacGregor and Grasch) assessing the implementation of an ERAS protocol containing gabapentin, in addition to evaluating the effect of pregabalin (Najafi Anaraki and Mirzaei 2014; Karami, Hoshyar, and Jafari 2021; El Kenany and El Tahan 2016; Grasch et al. 2023; MacGregor et al. 2021). These additional studies allowed the demonstration of an effect on MME at 300mg doses of gabapentin and pregabalin, findings not present in the previously mentioned SR-MA that showed efficacy using 600mg of gabapentin (Felder et al. 2019b).

CLINICAL IMPLICATIONS

Clinical utilization of gabapentinoids has long been a controversial topic in the literature. Despite demonstrating lower MMEs, pain scores, and nausea when used pre-operatively in abdominal hysterectomies (Alayed et al. 2014),

Table 1. Characteristics of included studies:

	Study location	Sample size*	Inclusion criteria	Exclusion criteria	Primary outcome	Intervention group	Control group	Timing of intervention
Randomized Control Trials:								
Moore et al (Moore et al. 2011).	Canada	44 (21 vs 23)	• Term • Scheduled CS • 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 h postop	600 mg oral gabapentin	Lactose placebo	1 h prior to surgery
Short et al (Short et al. 2011).	Canada	84 (42 vs 42)	• Term • Scheduled CS • 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 h postop	600 mg oral gabapentin	Lactose placebo	1 h prior to surgery
Nofal et al (Nofal, Mahmoud, and Al Alim 2014).	Egypt	86 (42 vs 44)	• Term • Scheduled CS • Singleton • Primiparous • Multiparous	• Chronic headaches • Chronic pain • Regular analgesics or antiepileptic medication use • Fetal congenital abnormalities	Post-dural puncture headache characteristics	600 mg oral gabapentin	Starch Placebo	2 h prior to surgery
Memari et al (Memari et al. 2015).	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 h (only antibiotics and sedatives)	VAS score for nausea and vomiting postop	600 mg oral gabapentin	Placebo	1 h prior to surgery
Monks et al (Monks et al. 2015).	Canada	197 (100 vs 97)	• Term • Scheduled CS • Ages 18-55	• Epilepsy • Chronic pain • Use of anticonvulsants or neuropathic anal-gesics • Opioid or IV drug abuser • Use of antacid in previous 3 hours	VAS pain on movement at 24 h postop	600 mg oral gabapentin	Lactose placebo	1 h prior to surgery

	Study location	Sample size*	Inclusion criteria	Exclusion criteria	Primary outcome	Intervention group	Control group	Timing of intervention
Hafez et al (Hafez et al. 2017).	Egypt	45 (15 vs 15)	• Term • Scheduled CS • 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	600 mg oral gabapentin	Placebo	1 h prior to surgery
Randolf et al (Randolf et al. 2019).	USA	13 (3 vs 10)	• GA: ≥30 weeks • Scheduled CS • Age ≥18	• Opiate abuse or Hx • Chronic pain • Hx of depression requiring meds • General anesthesia • Classical CS • MgSO4 use • Breastfeeding	MME	600 mg oral gabapentin	Starch Placebo	q8h for 48h postop
Anaraki et al (Najafi Anaraki and Mirzaei 2014).	Iran	78 (39 vs 39)	• Term • Primiparous • ASA physical status I or II • Scheduled CS	• Contraindications to neuraxial anesthesia • Smoking • Hepatitis • Drug use • Mental disorders • Severe preeclampsia • Fetal abnormalities • Diabetes	MME and VAS pain scores	300 mg oral gabapentin	10 µg of fentanyl intrathecally	2 h prior to surgery
Karami et al (Karami, Hoshyar, and Jafari 2021).	Iran	136 (68 vs 68)	• Scheduled CS	• Hx of Migraine • ASA III or IV • Hx of >1 dural puncture • Emergency CS indicated • Hx of PDPH • Contraindications of spinal anesthesia • Block failure • Adjuvant injection • CS-related complications • Loss to follow-up	VAS pain score	150 mg oral Pregabalin	Placebo	Night before spinal anesthesia
Kenani et al (El Kenany and El Tahan 2016).	Egypt	135 (45 vs 45 vs 45)	• Age 18-38 • ASA I or II • Singleton • GA >36 weeks	• Hx of chronic pain • Cardiovascular, pulmonary, hepatic, renal, endocrinal, neuropsychiatric illness • Prolonged PR interval • DM2 • Anemia	MME and VAS pain on movement and rest at 48 h postop	300 mg oral Pregabalin vs 150 mg oral Pregabalin	Sugar placebo	1 h prior to surgery

	Study location	Sample size*	Inclusion criteria	Exclusion criteria	Primary outcome	Intervention group	Control group	Timing of intervention
				• Bleeding/coagulation disorder • Thrombocytopenia • BMI ≥35 kg/m2 • IUGR • Gestational HTN • Taking pregabalin, anticonvulsants, antidepressants, antipsychotics, alcohol or drugs of abuse, NSAIDs, opioids or benzodiazepines				
Observational studies								
Ende et al. (Ende et al. 2022)	USA	214 (64 vs 150)	• CS • ≥1 dose of buprenorpine within 72 hrs of CD	• Postoperative ICU admission • Missing data on PCA • Discharged before 72 hrs stay	MME	Gabapentin	No gabapentin	Within 24 hours of CD
Macgregor et. al (MacGregor et al. 2021).	USA	144 (74 vs 70)	• PRE: repeat CS • Post: ERAS protocol with CS	• Chronic opioid use	MME	600 mg gabapentin (as part of ERAS protocol)	No ERAS protocol	Immediately before arriving to operating room
Grasch et. al (Grasch et al. 2023).	USA	128 (72 vs 56)	• CS (urgent and scheduled)	• IUFD • Cesarean hysterectomy • Chronic opioid use • Immediate PCA use postoperatively	MME	300 mg gabapentin (as part of ERAS protocol)	No ERAS protocol	Q6hrs for 48 hrs postop

CS: Cesarean Section, VAS: Visual Analog Scale, MME: Morphine Milligram Equivalents, HTN: Hypertension, DM: Diabetes Mellitus, NRS: Numerical pain Rating Scale, Hx: History, PDPH: Post Dural Puncture Headache, IUGR: Intra-Uterine Growth Restriction, PCA: patient-controlled analgesia, IUFD: intrauterine fetal demise.

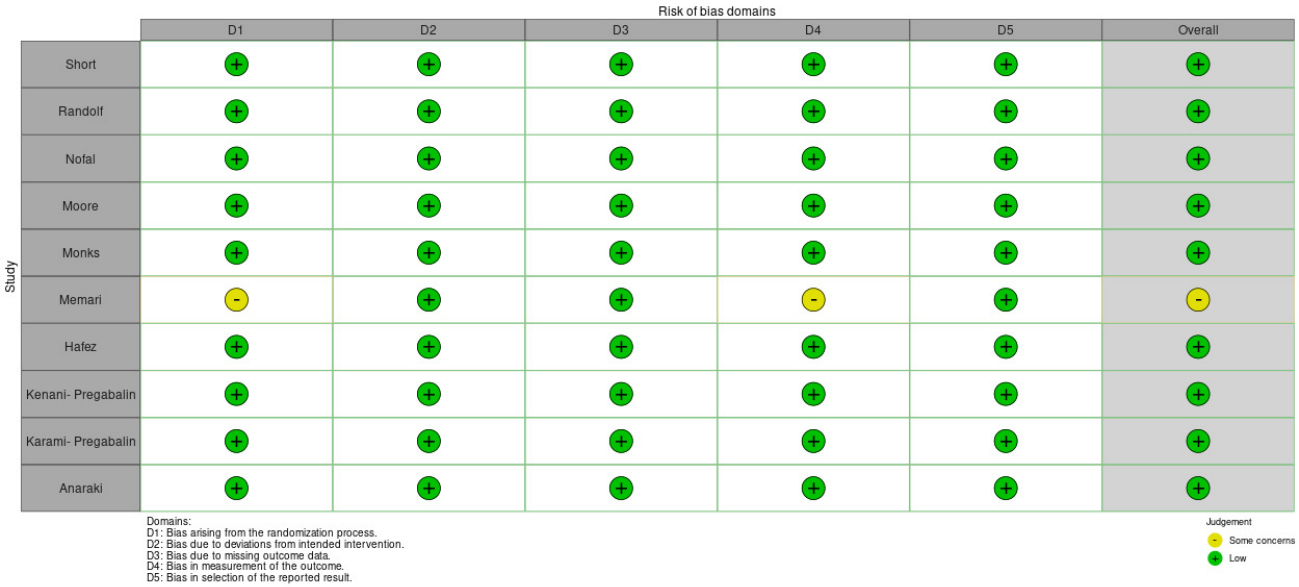

Figure 2. Risk of Bias assessment using Rob2 tool for RCTs.

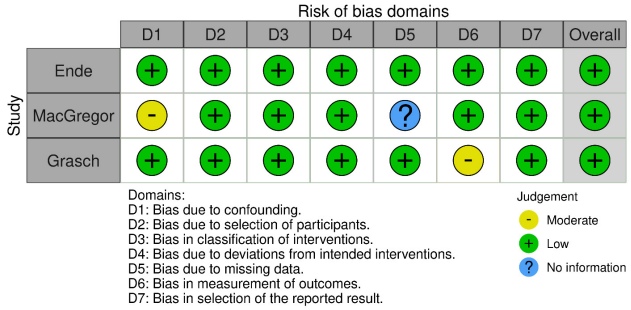

Figure 3. Risk of Bias assessment using Robins-I tool for observational studies.

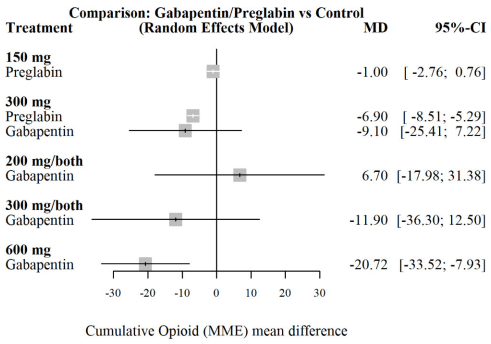

Figure 4. Network Meta-Analysis for Total Cumulative Opioids post-operative (MME) for RCT which used Gabapentin or Preglabin given perioperatively vs Control.

This includes 2 studies with pre-post design. Note: 'both' indicates Gabapentin was given before and after surgery. Results are mean difference (MD) and 95% confidence interval (CI)

multiple publications have been published opposing their use, citing statistically but not clinically relevant effects on postoperative pain, subacute pain and no effects on chronic postoperative pain in both gabapentin and pregabalin, regardless of administration timing. Most of these reviews did not support the routine use of gabapentinoids in the management of postoperative pain in adults (Verret et al. 2020; Eipe et al. 2015; Mishriky, Waldron, and Habib 2015; Fabritius et al. 2017b, 2017a; Goodman and Brett 2019).

ERAS pathways were developed to optimize patient outcomes by introducing interventions that were data supported (Kalogera and Dowdy 2016). ERAS implementation has shown promising results after for gynecologic oncology procedures, delivering improved clinical outcomes such as length of stay, complications, readmissions, and cost (Bisch and Nelson 2022). Going further, Meyer et. al. found a 72% reduction in mean opioid consumption among gynecologic oncology patients after the implementation of the ERAS protocol, in addition to 16% of patients achieving an opioid-free hospital stay without significant differences in pain scores (Meyer et al. 2018). Meyer et. al. also reported that the ERAS group had an earlier resolution of impairment in activities and return to walking (Meyer et al. 2018). Decreases in opioid consumption and pain scores were similarly observed in ERAS protocols that included gabapentin, in both pre-CS or pre- and post-CS administration (Grasch et al. 2023; MacGregor et al. 2021).

Implementation of ERAS protocols containing gabapentinoids would then, hypothetically, lead to safer pain control methods compared to opioids. One of the benefits of gabapentin is its mild side-effect profile when compared to opioids (Yasaei, Katta, and Saadabadi 2022). Additionally, gabapentin does not concentrate in breast milk, leading to low serum levels and no observed side effects in

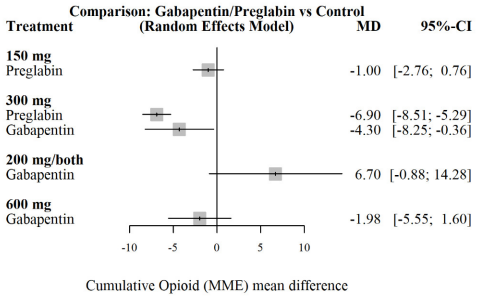

Figure 5. Network Meta-Analysis for Total Cumulative Opioids post-operative (MME) for RCT which used Gabapentin or Pregabalin given perioperatively vs Control.

This includes RCT only. Note: 'both' indicates Gabapentin was given before and after surgery. Results are mean difference (MD) and 95% confidence interval (CI).

breastfed infants (Ohman, Vitols, and Tomson 2005; Kristensen et al. 2006). Pregabalin has also been described as moderately safe during breastfeeding (Hale and Rowe 2016). Side effects mentioned in studies analyzed included sedation, nausea, vomiting, dizziness, and blurred vision (Nofal, Mahmoud, and Al Alim 2014; Monks et al. 2015; Hafez et al. 2017; Karami, Hoshyar, and Jafari 2021; El Kenany and El Tahan 2016). In light of these findings, an RCT designed by Memari et. al. evaluated the effect of 600mg of Gabapentin pre-op on post-CS nausea and vomiting (Memari et al. 2015). The double-blind, placebo-controlled trial demonstrated significantly lower nausea severity at 1hr postop (p= 0.041), with lower incidence of vomiting (p=0.048) in the Gabapentin group (Memari et al. 2015).

RESEARCH IMPLICATIONS

Whether gabapentin or pregabalin is the optimal choice for CS ERAS regimens has not been well examined. The included RCTs by El Kenany and Karami both compared pregabalin to placebo (Karami, Hoshyar, and Jafari 2021; El Kenany and El Tahan 2016). However, we were unable to locate any trials comparing gabapentin to pregabalin directly. The use of a network approach to the meta-analysis allowed for indirect comparisons of gabapentin and pregabalin. In our network analysis limited to RCTs, 300mg doses of pregabalin and gabapentin demonstrated similar reductions in consumed MMEs. A trial directly comparing the two drugs may be warranted.

Table 2. Characteristics of the included study participants in randomized controlled trials

	Maternal Age	GA at randomization	BMI (kg/m2)
Moore et al.	35 ± 5 vs 34 ± 6	38.8 ± 0.7 vs 38.9 ± 0.8	29 ± 4 vs 30 ± 6
Short et al.	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.	32.1 ± 4.8 vs 30.7 ± 5.2	Not reported	Not reported
Memari et al.	26.1 ± 5.2 vs 26.1 ± 5.2	38.2 ± 0.5 vs 38.1 ± 0.4	Not reported
Monks et al.	35.9 ± 3.9 vs 34.7 ± 4.5	38.7 ± 0.8 vs 38.6 ± 0.9	30.8 ± 5.1 vs 31.3 ± 5.6
Hafez et al.	28.2 ± 4.7 vs 27.3 ± 5.5	38.3 ± 1.1 vs 38.1 ± 1.0	Not reported
Randolf et al.	35.3 ± 5.5 vs 30.1 ± 5.1	37.3 ± 1.8 vs 38.3 ± 1.7	33.3 ± 4.4 vs 39.6 ± 12.5
Anaraki et al.	27 ± 4 vs 28 ± 4	37.3 ± 1.3 vs 37.5 ± 1.1	28 ± 3 vs 29 ± 3
Karami et al.	28.5 ± 5.78 vs 27.15 ± 5.73	Not reported	Not reported
Kenani et al.	27.3 ± 4.94 vs 28.2 ± 4.99 vs 26.7 ± 5.61	38.4 ± 1.90 vs 38.0 ± 1.10 vs 38.5 ± 1.14	28.9 vs 29.7 vs 29.6 *

* Authors provided Height and Weight, BMI was calculated
Data are presented as mean ± standard deviation

Table 3. League table for pairwise comparisons from random effects model using only RCT data for total cumulative opioids (MME) by dose for Gabapentin, corresponds to Figure 5.

200 mg/both	--	--	**6.70 (-0.88 to 14.28)**
11.00 (2.46 to 19.55)	**300 mg**	-1.00 (-7.73 to 5.73)	-4.28 (-8.30 to -0.27)
8.68 (0.29 to 17.06)	-2.33 (-7.16 to 2.50)	**600 mg**	-1.67 (-5.34 to 2.00)
6.70 (-0.88 to 14.28)	-4.30 (-8.25 to -0.36)	-1.98 (-5.55 to 1.60)	**Control**

Note: network estimates provided in lower triangle and direct treatment estimates in upper triangle.

STRENGTH AND LIMITATIONS

A strength of our study is that the methodology followed was compliant with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2019). Limitations of this study include different dosing and scheduling regimens for gabapentinoids used in the studies (pre-op vs both pre- and post-op), which may have limited the ability to demonstrate some significant differences and to synthesize results from different studies. There was also some inconsistency in the dose findings, likely due to smaller numbers in different dosing groups. Additional limitations include the limited sample sizes of studies included, non-uniformity such as in inclusion and exclusion criteria amongst studies evaluated, and lack of information regarding duration of surgery, or presence/absence of adhesions. A clear research priority should be harmonization of gabapentin regimens for CS ERAS protocols, as well as measurement standardization for outcomes, including participant satisfaction. While the inclusion of observational studies removes some ability to discuss causation, these represent some "real world" implementation using the drug and can help add to the evidence base. Additionally, outside of the observational studies, only the small Randolf trial used gabapentin continuing into the postoperative period (Randolf et al. 2019).

CONCLUSION

In conclusion, implementation of ERAS protocols including gabapentin or pregabalin may decrease total MME requirements in patients undergoing CS. Reducing MME, even in small increments, can be important in postoperative care. Gabapentinoids may also safely provide lower pain scores and improve satisfaction rates among patients. Given these findings, a large, multicenter trial is likely warranted to find the optimal ERAS gabapentin regimen to reduce opioid use after CS.

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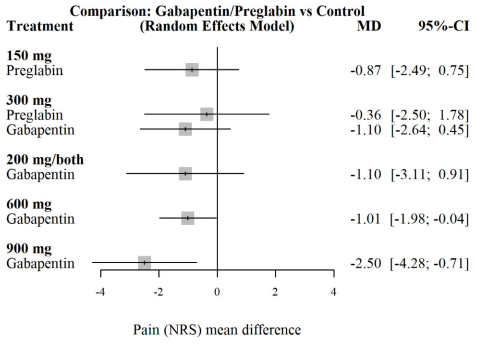

Figure 6. Network Meta-Analysis for pain on movement at 24 hours (NRS) for studies which used Gabapentin or Pregabalin given perioperatively vs Control.

This includes RCT only. Note: 'both' indicates Gabapentin was given before and after surgery. Results are mean difference (MD) and 95% confidence interval (CI).

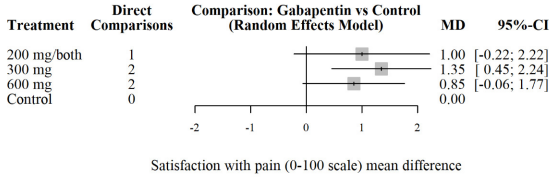

Figure 7. Network Meta-Analysis for Satisfaction with Pain (0-100 scale) for RCT which used Gabapentin given perioperatively vs Control.

This includes RCT only. Note: 'both' indicates Gabapentin was given before and after surgery.

Table 4. League table for pairwise comparisons from random effects model using only RCT data for Pain (NRS) by dose for Gabapentin, corresponds to Figure 6.

200 mg/both	--	--	--	**-1.10 (-3.11 to 0.91)**
-0.00 (-2.54 to 2.53)	**300 mg**	-0.60 (-2.75 to 1.55)	--	-0.74 (-2.39 to 0.92)
-0.09 (-2.33 to 2.14)	-0.09 (-1.74 to 1.56)	**600 mg**	0.90 (-1.08 to 2.88)	-0.99 (-1.97 to 0.00)
1.40 (-1.29 to 4.08)	1.40 (-0.89 to 3.70)	1.49 (-0.29 to 3.27)	**900 mg**	-3.10 (-5.09 to -1.11)
-1.10 (-3.11 to 0.91)	-1.10 (-2.64 to 0.45)	-1.01 (-1.98 to -0.04)	-2.50 (-4.28 to -0.71)	**Control**

Note: network estimates provided in lower triangle and direct treatment estimates in upper triangle.

Table 5. League table for pairwise comparisons from random effects model using only RCT data for Satisfaction for Pain (0-100) by dose for Gabapentin, corresponds to Figure 7.

200 mg/both	--	--	**1.00 (-0.22 to 2.22)**
-0.35 (-1.86 to 1.16)	**300 mg**	0.20 (-1.13 to 1.53)	1.34 (0.41 to 2.26)
0.15 (-1.38 to 1.67)	0.50 (-0.59 to 1.58)	**600 mg**	0.70 (-0.25 to 1.64)
1.00 (-0.22 to 2.22)	1.35 (0.45 to 2.24)	0.85 (-0.06 to 1.77)	**Control**

Note: network estimates provided in lower triangle and direct treatment estimates in upper triangle.

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SUPPLEMENTARY MATERIALS

Supplemental Figure 1. Network Meta-Analysis for pain on movement at 24 hours (NRS) for studies which used Gabapentin or Preglabin given perioperatively vs Control.

Download: https://www.napgo.org/article/140819-a-systematic-review-and-network-meta-analysis-of-the-use-of-gabapentinoids-perioperatively-at-the-time-of-cesarean-for-reducing-opioid-use/attachment/288983.tiff