Can J Anesth/J Can Anesth (2020) 67:817–826
https://doi.org/10.1007/s12630-020-01582-y

REPORTS OF ORIGINAL INVESTIGATIONS

The effect of intravenous dexamethasone on postoperative nausea and vomiting after Cesarean delivery with intrathecal morphine: a randomized-controlled trial

Effet de la dexaméthasone intraveineuse sur les nausées et vomissements postopératoires après un accouchement par césarienne avec morphine intrathécale : un essai randomisé contrôlé

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Received: 24 July 2019 / Revised: 26 December 2019 / Accepted: 28 December 2019 / Published online: 27 January 2020

Abstract

Purpose *Intrathecal morphine administered during spinal anesthesia for Cesarean delivery is associated with a high incidence of postoperative nausea and vomiting (PONV). Small studies performed to date provide conflicting evidence on the effectiveness of dexamethasone as prophylaxis in this setting, raising the possibility that efficacy may be linked to dose timing. This study hypothesized that intravenous dexamethasone given prior to intrathecal morphine during spinal anesthesia may reduce the incidence of PONV.*

Methods *In this double-blind, placebo-controlled trial, 108 patients undergoing Cesarean delivery were randomized to receive 8 mg dexamethasone or placebo prior to spinal anesthesia that included 0.2 mg intrathecal morphine. Outcomes were assessed on postanesthesia care unit arrival, as well as at postoperative hours one, three, six, 24, and 48. The primary outcome was the total number of subjects experiencing PONV during the study period of 48 hr postpartum. Secondary outcomes included severity of pain via the numeric rating scale pain score, and the use of rescue antiemetics and analgesics.*

Results *No significant difference in the number of patients experiencing PONV was found between the treatment (n = 44, 80.0%) and control groups (n = 45, 84.9%) (difference -4.9%; 95% confidence interval, -19.2 to 9.4; P = 0.50), nor for median numeric rating scale pain scores (P = 0.24), total consumption of rescue antiemetics (P = 0.40), or opioid analgesics (P = 0.26).*

Conclusions *This trial does not support the use of dexamethasone prior to intrathecal morphine for PONV prophylaxis in Cesarean delivery.*

Trial registration *www.clinicaltrials.gov (NCT01734161); registered 27 November, 2012.*

Résumé

Objectif *La morphine intrathécale administrée au cours de la rachianesthésie pour un accouchement par césarienne est associée à une forte incidence de nausées et vomissements postopératoires (PONV). Les petites études menées à ce jour ont fourni des données probantes contradictoires sur l'efficacité de la prophylaxie par dexaméthasone dans ce contexte, soulevant la possibilité que son efficacité soit liée au moment de l'administration. Les auteurs de cette étude ont fait l'hypothèse que la dexaméthasone intraveineuse administrée avant la morphine intrathécale au cours*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12630-020-01582-y) contains supplementary material, which is available to authorized users.

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d'une rachianesthésie pouvait réduire l'incidence des PONV.

Méthodes *Dans cette étude en double insu, contrôlée contre placebo, 108 patientes subissant un accouchement par césarienne ont été randomisées pour recevoir 8 mg de dexaméthasone ou un placebo avant une rachianesthésie qui incluait 0,2 mg de morphine intrathécale. Les résultats ont été évalués à l'arrivée dans l'unité de soins post anesthésie ainsi qu'à 1, 3, 6, 24 et 48 heures postopératoires. Le critère d'évaluation principal était le nombre de patientes éprouvant des PONV au cours de la période d'étude de 48 heures post-partum. Les critères d'évaluation secondaires étaient, notamment, la sévérité de la douleur établie par le score de douleur sur une échelle d'évaluation numérique, et le recours aux antiémétiques et analgésiques de secours.*

Résultats *Aucune différence significative n'a été constatée sur le nombre de patientes éprouvant des PONV entre le groupe recevant le traitement (n = 44; 80,0 %) et le groupe contrôle (n = 45; 84,9 %) (différence -4,9 %; intervalle de confiance à 95 % : -19,2 % à 9,4%; P = 0,50). Il n'y a pas eu non plus de différences dans les scores de douleur avec l'échelle d'évaluation numérique (P = 0,24) et la consommation totale de médicaments de secours, antiémétiques (P = 0,40) ou narcotiques (P = 0,26).*

Conclusions *Cette étude ne soutient pas l'utilisation de dexaméthasone avant l'administration de morphine intrathécale pour la prophylaxie des PONV dans l'accouchement par césarienne.*

Enregistrement de l'essai clinique *www.clinicaltrials.gov (NCT01734161); enregistré le 27 novembre 2012.*

For patients undergoing Cesarean delivery, the incidence of intra- or postoperative nausea and vomiting (PONV) is high, with estimates ranging from 30% to 80%.[1] Studies in the Cesarean delivery population evaluating patient concerns have found that avoiding nausea and vomiting rates second only to avoiding pain during and after surgery.[2]

The etiology of nausea and vomiting in this population is multifactorial. Hypotension, vagal activity, bleeding, uterotonics, exteriorization of the uterus, antibiotics, and movement of the patient all may have emetogenic effects.[1] Administration of intrathecal morphine provides long acting analgesia, but is associated with a three- to five-fold increase in PONV compared with a non-opioid containing spinal anesthetic.[3]

A meta-analysis investigating the role of intravenous dexamethasone as a prophylactic agent in patients receiving neuraxial morphine only found a significant decrease in incidence of PONV in the group receiving *epidural* morphine. It did not observe a decrease in the group receiving *intrathecal* morphine.[4] Of note, in the six randomized-controlled trials (RCTs) included in that meta-analysis where morphine was delivered through the epidural route, intravenous dexamethasone was administered prior to epidural morphine. Nevertheless, in the two small multi-arm RCTs included where morphine was delivered intrathecally, the intravenous dexamethasone was administered prior to the end of surgery, not prior to the actual intrathecal injection of morphine.[5,6] These results raise the question as to whether the timing of intravenous dexamethasone prior to neuraxial morphine is important.[4] To our knowledge, no study prior to this one has evaluated the efficacy of intravenous dexamethasone administered prior to intrathecal morphine.

Since publication of the above meta-analysis, a third RCT was performed which reported a beneficial effect of intravenous dexamethasone given following intrathecal morphine. This effect was only noted in a secondary analysis where the cumulative incidence of PONV was analyzed and was not significant at any time point.[7] That RCT, as well as twelve other RCTs where morphine was administered either through the epidural or intrathecal route, was incorporated into a more recent meta-analysis, which found a reduction in PONV when intravenous dexamethasone was administered to patients receiving neuraxial morphine.[8] Nevertheless, this meta-analysis included studies with high bias risk and did not present a subgroup analysis for intrathecal administration or Cesarean delivery patients. Therefore, the literature currently supports the use of intravenous dexamethasone for PONV prophylaxis in patients receiving epidural morphine, but it remains unclear if it provides a benefit with intrathecal morphine for Cesarean delivery.

To better establish whether dexamethasone provides effective prophylaxis for PONV associated with intrathecal morphine and to assess whether the timing of intravenous dexamethasone administration is important, we performed an RCT in which patients undergoing Cesarean delivery received intravenous dexamethasone or placebo prior to intrathecal morphine. The primary outcome measure was the total number of patients experiencing PONV during the first 48 postpartum hr. We hypothesized that the administration of dexamethasone prior to intrathecal morphine would result in a significant decrease in PONV. Secondary outcomes were PONV impact scores, numeric rating scale (NRS) pain scores, and total dosages of rescue antiemetics and analgesics administered.

Methods

The Institutional Review Board of Weill Cornell Medicine provided ethical approval for this trial (protocol number 1207012632, approved October 23 2012). The study was registered at clinicaltrials.gov (NCT01734161, approved November 27 2012). Written informed consent was obtained from all subjects entering the trial. Subjects were recruited either in person during their preoperative laboratory visit or via telephone prior to their date of surgery. The study was a randomized, double-blinded, placebo-controlled, trial conducted at a single centre (New York-Presbyterian Hospital/Weill Cornell Medicine in New York, NY, USA) between November 2012 and September 2014. The CONSORT recommendations for reporting randomized-controlled clinical trials were followed.[9]

Selection and description of participants

Inclusion criteria were women with American Society of Anesthesiologists physical status II, aged 18–46 yr, presenting for scheduled primary or repeat Cesarean delivery of a viable fetus under spinal anesthesia (with or without epidural catheter insertion) including intrathecal morphine. Exclusion criteria were use of antiemetics in the 24 hr prior to presentation, an allergy to dexamethasone or morphine, and a history of gastrointestinal disease, diabetes, hypertension, or hyperemesis gravidarium. Subjects were recruited prior to the date of their Cesarean delivery.

Intraoperatively, patients with greater than one liter of estimated intraoperative blood loss, sustained hypotension (as defined as a mean arterial pressure < 60 mmHg for more than ten minutes), or a conversion to a general anesthetic were withdrawn from the study.

Procedures

A randomization table prepared by the New York-Presbyterian Hospital investigational pharmacy allocated subjects using a computer-generated simple (non-blocked) random number sequence. After randomization, the study drug (8 mg of dexamethasone in 50 mL normal saline) or placebo (50 mL normal saline) was prepared by an unblinded investigator who had no further involvement in the study. Placebo and study drug were identical in appearance and marked only with the study participant's allocated number. All subjects, care providers, and data collectors were blinded to allocation. The randomization code was broken only following completion of subject enrolment and all data collection.

Following placement of an intravenous catheter by the obstetrical nurse, and prior to the patient being brought into the operating room, the patient received either the study medication or placebo via an infusion over ten minutes. This infusion rate has been reported to reduce the side effects of perineal flushing and pruritus, which may result from an intravenous bolus.[10] No patients reported side effects from the medication.

Spinal anesthesia was administered in the operating room with hyperbaric 0.75% bupivacaine (total dose as per the discretion of the attending anesthesiologist), 200 μg of morphine and 20 μg of fentanyl. Electrocardiography and pulse oximetry were measured continuously, and blood pressure was measured via a non-invasive blood pressure cuff. Blood pressure was initially recorded with the patient in a sitting position and then with the patient in a dorsal supine position with left uterine displacement every two to five minutes. All vital sign data were automatically entered into the electronic medical record (CompuRecord, Philips Healthcare USA, Andover, MA, USA).

Standard surgical practice at our institution is to perform a Cesarean delivery using a Pfannestiel skin incision and transverse uterine incision in the lower uterine segment. Following delivery of the infant, patients received oxytocin as a uterotonic via an intravenous infusion in a 1 L bag of crystalloid fluid. The rate of administration was manually titrated by the anesthesia team and total number of units administered determined by the volume given. No participants required administration of an alternate uterotonic (methylergonovine or carboprost).

From the intraoperative record, the three lowest blood pressures were noted for each patient. Blood pressure control was achieved either by phenylephrine boluses, phenylephrine infusion, or ephedrine boluses or a combination thereof, as per the discretion of the anesthesia team. The total administration of intravenous phenylephrine and ephedrine was noted from the medical record. Fluid administration was handled at the discretion of the anesthesia team. Only patients who reported nausea or vomiting to their anesthesia team received intraoperative antiemetics, which was recorded. Ondansetron (4–8 mg) was the agent used for all patients requiring an antiemetic intraoperatively.

Oral ibuprofen 800 mg was administered every eight hours postoperatively. In patients unable to tolerate oral medications, intravenous ketorolac 15 mg was administered for three doses every eight hours. Additional opioid analgesics were ordered by the obstetrician and administered only when requested by patients. One to two tablets of oral oxycodone/acetaminophen (5/325 mg) or oxycodone IR (5 mg) were given every four hours as per patient request. At patient request, intravenous ondansetron 4 mg was given every six

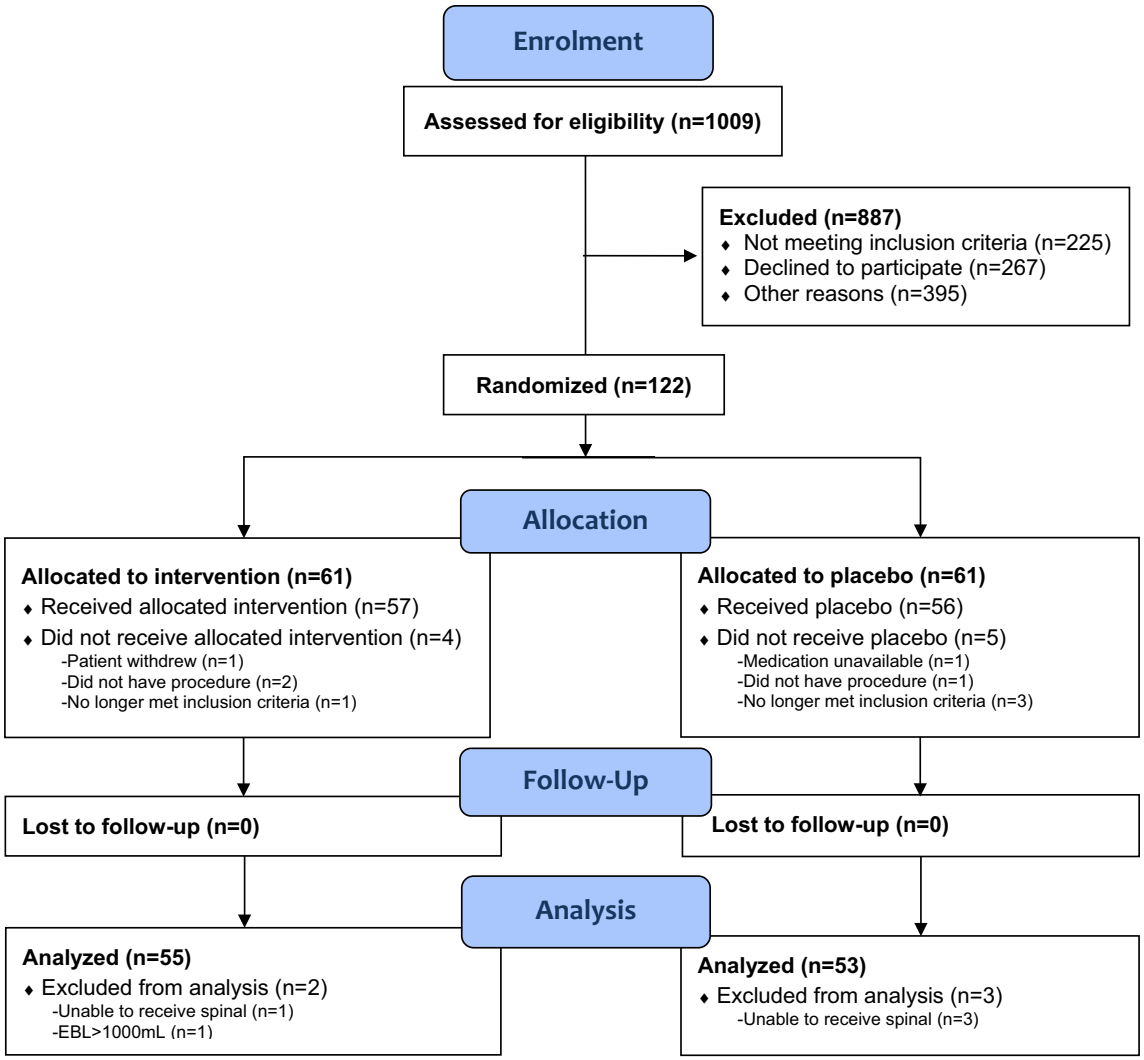

Figure CONSORT flow diagram

hours for nausea or vomiting and intravenous nalbuphine 5 mg was given every eight hours up to three total doses for pruritus.

Measurements

For each patient, the following demographics were obtained prior to allocation: age, ethnicity, height, weight, gravidity, parity, gestational age, non-smoking status, and history of PONV or motion sickness. Whether the Cesarean delivery was a primary or repeat was also noted, as well as any past medical history.

Postoperative variables were collected in the postanesthetic care unit (PACU) upon arrival (t = 0) and then at one, three, six, 24, and 48 hr following PACU arrival, either in the PACU or, once discharged from recovery, in the patient's inpatient hospital room. All assessments were performed by an investigator blinded to treatment allocation. All patients were assessed for the same variables and answered the same Institutional Review Board-approved questions.

Postoperative nausea and vomiting was assessed using the simplified PONV impact scale described by Myles and Wengritzky.[11] Patients were asked to assess their nausea and vomiting severity according to the scale for the time frame between assessments. The PONV impact score is a numeric rating score derived from the sum of two questions, resulting in a numerical score from 0 to 6. The first question rates the subject's frequency of vomiting or dry-retching from 0 to 3 (0 for no instances, 1 for once, 2 for twice, and 3 for three or more instances). The second question rates the amount of time a subject experiences nausea from 0 to 3 (0 for never nauseous, 1 for nauseous some of the time, 2 for most of the time, and 3 for all of the time).[11] Therefore, with any score $\geq$ 1, nausea was considered to be present. The PONV rating tool used for

data collection is included in the Electronic Supplementary Material (ESM) eTable 1.

The NRS pain score was recorded during each visit to assess the subject's pain. The NRS consists of an 11-point horizontal line marked from 0 to 10, where 0 indicates "no pain," 5 indicates "moderate pain," and 10 indicates "worst possible pain". Subjects were asked by an investigator to indicate where their pain scored on that scale.

From the electronic medical record, the amount and dosage of antiemetics and opioid analgesics administered were recorded.

Statistical analysis

Based on the incidence reported in a recent meta-analysis,[4] we estimated the incidence of PONV in our population to be 53%. Sample size was calculated to detect a clinically meaningful 50% difference in PONV in the treatment group, applying the Chi square test without continuity correction. Assuming a two-tailed type I error rate of 0.05 ($\alpha = 0.05$), and type two error rate of 0.20 ($1\text{-}\beta = 0.80$), a total sample size of 108 evaluable subjects ($n = 54$ per group) would be required.

The primary outcome measure was the total number of subjects in the 48-hr study period who experienced PONV, which includes patients who experienced postoperative nausea alone (PON) and those with vomiting (POV). Secondary outcomes included the simplified PONV impact scores and NRS pain scores (both measured upon PACU arrival and one, three, six, 24, and 48 hr following). Median PONV impact scores were calculated for each subject using their PONV impact score data from the entire postoperative period. Median NRS pain scores were calculated in the same manner. The overall PONV impact score (Table 2) is the median of the subjects' median PONV impact scores over the 48-hr study period; the overall median NRS pain score is calculated similarly. The administration of rescue antiemetics (ondansetron) and the total dosage of opioid analgesics (converted to oxycodone equivalents) were also assessed as secondary outcomes.

To assess differences in intra- and postoperative variables between the dexamethasone and control groups, we conducted independent two-sample t tests, Mann–Whitney U tests, and Pearson's Chi square tests, as appropriate. Normality was assessed with skewness-kurtosis tests. To assess any effect of potential correlated observations within subjects in longitudinal measures, we conducted repeated measures analysis of variance. A two-sample test of proportions with an estimated large-sample variance was used to calculate the 95% confidence interval (CI) for the difference in proportions between groups.

To adjust for potential confounding, we used multivariable logistic regression analyses to calculate adjusted odds ratios and 95% CIs. Separate models were used to predict the primary outcomes of POV, PON, and PONV. Multivariable analyses included variables that differed between treatment and placebo groups at a significance level of $P \leq 0.25$ in bivariate analyses. Additional variables known to modify PONV were also included in multivariable analyses. These variables were a history of PONV or motion sickness, total fluid inputs, total amount of intraoperative ephedrine and phenylephrine (in phenylephrine equivalents), total amount of intraoperative oxytocin, and the nadir systolic blood pressure. All multivariable models were tested for collinearity and assessed for goodness-of-fit with the Hosmer–Lemeshow test with ten groups.

An all-subjects-as-treated analysis was applied. To assess robustness and evaluate for any bias introduced by exclusions and missing data, we performed a sensitivity analysis of the primary outcome. Here, we assumed two extreme-case scenarios: that all non-evaluated subjects in the treatment group had PONV and all in the control group did not, and vice versa. The Fisher–Boschloo unconditional exact test was applied. Further, to assess the sensitivity of the logistic regression analyses to any overfitting, we reran the model with only the known predictor variables included.

All analyses were conducted in Stata IC, Version 13 (StataCorp, College Station, TX, USA). Statistical significance was evaluated at the 0.05 alpha level.

Results

Out of 1,009 total patients screened, 614 met eligibility criteria, and 389 patients were approached for participation in this study. Reasons for not approaching 225 eligible patients included failure to notify research staff of patient arrival, research investigators unavailable to consent, and delivery of fetus prior to the scheduled surgery. The CONSORT flow diagram is shown in the Figure.

Of the patients approached, 122 patients agreed to participate and were randomized into the study (dexamethasone group $n = 61$, placebo group $n = 61$). Fourteen patients were withdrawn from analysis (see Figure). A total of 108 evaluable subjects were included in the analysis (dexamethasone group $n = 55$, placebo group $n = 53$). Subjects were recruited until $n = 108$ were obtained, as this was the estimated sample size needed to detect an effect of dexamethasone on PONV.

There were no significant differences in baseline patient characteristics between the dexamethasone and placebo groups (Table 1). There were no significant inter-group

Table 1 Patient demographics and intraoperative characteristics

	Placebo group (n = 53)	Dexamethasone group (n = 55)
Age, (yr) (SD)	35.7 (3.7)	35.4 (5.2)
BMI, ($kg \cdot m^{-2}$) [IQR]	26.8 [24.8–30.2]	27.7 [25.8–31.6]
Gestational age, (weeks) [IQR]	39.1 [39–39.3]	39.1 [39–39.4]
Primary Cesarean delivery, n (%)	17 (32%)	26 (47%)
History of PONV or motion sickness, n (%)	6 (11.3%)	8 (14.5%)
History of current tobacco use, n (%)	0 (0%)	0 (0%)
Baseline heart rate, ($beats \cdot min^{-1}$) [IQR]	81 [74–94]	86 [75–95]
Duration between administration of study drug and intrathecal morphine, (min) [IQR]	22 [13–35]	22 [17–32]
Duration between administration of study drug to end of procedure, (min) [IQR]	75 [63–101]	80 [68–93]
Total operative time, (min) [IQR]	42 [34–51]	45 [33–53]
Intrathecal bupivacaine administered, (mg) [IQR]	12 [12–12]	12 [12–12]
Patients receiving intraoperative ondansetron, n (%)	14 (26.4%)	24 (43.6%)
Intraoperative nausea or vomiting, n (%)	14 (26.4%)	24 (43.6%)
Total intraoperative vasopressor dose, (in μg of phenylephrine)* [IQR]	560 [320–1080]	480 [120–1080]
Mean of three lowest recorded intraoperative systolic blood pressures, (mmHg) (SD)	95.6 (12.3)	93.3 (13.0)
Total oxytocin administered, (U) [IQR]	20 [16–20]	20 [14–20]
Estimated blood loss, (mL) [IQR]	800 [800–800]	800 [800–800]
Total crystalloid fluid input (mL) (SD)	1852 (652)	1865 (526)
Ketorolac administered intraoperatively, n (%)	11 (20.8%)	13 (23.6%)

Number (%) and medians [interquartile range] reported, as appropriate.

*For total intraoperative vasopressor dose, 1 mg of ephedrine was considered equivalent to 16 μg of phenylephrine.

BMI = body mass index; IQR = interquartile range; PONV = postoperative nausea and vomiting; SD = standard deviation.

differences in intraoperative characteristics known to modify the risk of nausea and vomiting (namely hypotension or fluid administration). Estimated blood loss (EBL) ranged from 600 to 1,000 mL; the majority of subjects (98/108) had an EBL of 800 mL. The other ten subjects were evenly distributed between the placebo and study groups. All study patients received intravenous infusion of oxytocin and no additional uterotonics were administered to any study patients.

No patient received narcotics or local anesthetics administered via the epidural route.

Following delivery of the placenta, the uterus is commonly exteriorized and returned to the abdomen when adequate hemostasis is obtained. Nevertheless, the exteriorization of the uterus was not recorded by study personnel. Neither was this information included in the operative notes of 17 study patients (eight in placebo group, nine in dexamethasone group). In the patients for whom the exteriorization of the uterus was described in the operative notes, there were 43 placebo group patients and 37 dexamethasone group patients. Of those for whom the uterus was noted to remain in situ, there was one placebo group patient and nine dexamethasone group patients.

Only participants reporting nausea or vomiting intraoperatively were given ondansetron. Therefore, the number of patients with intraoperative nausea and/or vomiting (IONV) and those receiving intraoperative ondansetron were the same. A higher percentage of patients with IONV was observed in the study group compared with placebo, but this difference was not significant.

Primary outcome: postoperative nausea and vomiting

The majority of patients in both groups reported either nausea and/or vomiting during at least one assessment and there was no statistically significant difference between groups. Over the entire study period, 80.0% of patients in the study group experienced PONV compared with 84.9% of the patients in the placebo group (difference, 4.9%; 95% CI, -19.2 to 9.4; $P = 0.50$) (Table 2). In the dexamethasone group, 29 subjects (52.7%) experienced at least one emesis episode with nausea (POV) at any point in the 48-hr postoperative assessment period, and 24 subjects in the placebo group (45.3%) experienced the same; the difference between groups was not statistically significant

Table 2 Outcomes throughout the 48-hr postoperative period

	Placebo group (n = 53)	Dexamethasone group (n = 55)	Difference (95% CI)	P value
Incidence of nausea and vomiting:				
Nausea only (PON), n (%)	21 (39.6%)	15 (27.3%)	-12.3% (-30.0 to 5.3)	0.17
Nausea with vomiting (POV), n (%)	24 (45.3%)	29 (52.7%)	7.4% (-11.4 to 26.3)	0.44
Total (PONV), n (%)	45 (84.9%)	44 (80.0%)	-4.9% (-19.2 to 9.4)	0.50
Overall PONV impact score [IQR]	0 [0–0.5]	0 [0–1]	-	0.69
PONV impact score $\geq$ 5 at any time point, n (%)	5 (9.4%)	7 (12.7%)	-	0.59
Total # of emesis episodes [IQR]	0 [0–3]	1 [0–3]	-	0.61
Patients requiring rescue antiemetics, n (%)	18 (34%)	17 (31%)	-	0.74
Total ondansetron administered (mg) [IQR]	0 [0–4]	4 [0–4]	-	0.14
Overall NRS pain score [IQR]	2 [1–3.25]	1.5 [0–3.25]	-	0.24
Total ibuprofen administered (g) [IQR]	3.2 [2.4–4.0]	3.2 [2.4–4.0]	-	0.18
Total ketorolac administered (mg) [IQR]	30 [30–45]	30 [30–45]	-	0.98
Total acetaminophen administered (mg) [IQR]	3250 [1300–4875]	3900 [1300–5200]	-	0.82
Total opioids administered (mg of oxycodone) [IQR]	75 [40–100]	65 [35–90]	-	0.26

Number (%) and medians [interquartile range] reported as appropriate. Percent difference in sample proportions (95% confidence interval) reported for primary outcomes.

CI = confidence interval; IQR = interquartile range; NRS = numeric rating scale; PONV = postoperative nausea and vomiting; POV = postoperative vomiting.

(P = 0.44). This null finding held when assessing the total number of subjects' that reported nausea without vomiting (PON) within the 48-hr study period, 15 subjects in the dexamethasone group (27.3%) and 21 in the placebo group (39.6%) (P = 0.17). No adjustment for multiple comparisons was made in the three primary outcomes.

In the multivariable analysis, which included any variables identified in bivariate analysis with $P < 0.25$ (body mass index, history of prior Cesarean delivery, baseline heart rate, amount of intraoperative ondansetron administered, and EBL) as well as known risk factors for PONV, there was no significant treatment effect on the outcome of PONV, POV, or PON (eTable 2 in the ESM). Nevertheless, it must be noted that the CIs were wide. The odds ratios associated with treatment were 0.64 (95% CI, 0.21 to 1.99) for PONV; 1.02 (95% CI, 0.43 to 2.40) for POV; and 0.57 (95% CI, 0.23 to 1.46) for PON. No models exhibited collinearity, and all were well-fitted. The results were robust when the model was rerun with only known predictor variables.

In the sensitivity analysis, the results withstood extreme assumptions for excluded subjects and missing data. There was no significant difference when it was assumed that all excluded subjects in the treatment group had PONV and those in the control group did not (P = 0.32), nor when it was assumed that all excluded subjects in the control group had PONV and those in the treatment group did not (P = 0.06).

Secondary outcomes

We found no difference between groups in any measure of nausea and vomiting. PONV impact scores did not statistically differ significantly at any time point (Table 2) nor did they differ when comparing overall PONV impact scores or with a repeated measures design (treatment-by-time F (5,530) = 2.17, P = 0.06) (Table 2). Similarly, no significant difference was found between groups in the number of subjects having clinically significant PONV at any time during the study (defined by Myles and Wengritzky [11] as a PONV impact score of 5 or 6), number of emesis episodes, or need for rescue antiemetics (Table 2).

We found no statistically significant differences in NRS pain scores at all postoperative time points, both when analyzed independently or with a repeated measures design (treatment-by-time F (5,530) 0.96, P = 0.44) (Table 2). There was no statistically significant difference between groups in overall NRS pain score during the entire study period, nor in the dose of rescue analgesic administered (oxycodone and hydromorphone, measured in equivalent milligrams of oxycodone). One patient with an intolerance to oxycodone received intravenous hydromorphone 0.4 mg. Likewise, there was no significant difference between groups on dose of acetaminophen, ibuprofen, or ketorolac (Table 2) .

Discussion

The principal finding of this study is that the administration of 8 mg of dexamethasone prior to 0.2 mg of intrathecal morphine in patients presenting for scheduled Cesarean delivery did not significantly reduce PON, POV, or PONV. Further, it did not reduce PONV impact scores or the need for rescue antiemetic at any time point. Therefore, the primary and secondary hypotheses that early administration of dexamethasone reduces the incidence of PONV and the severity of PONV impact scores are not supported by these results.

Administration of intravenous dexamethasone as a prophylactic agent in parturients has been investigated secondary to its effective use in the context of non-obstetric general anesthesia.[12] A key aspect of this study was the timing of the dexamethasone administration. Allen *et al.*[4] had previously postulated that the lack of dexamethasone efficacy observed in two prior RCTs[5,6] might be because dexamethasone was administered after intrathecal morphine. The present study was designed to address the question of whether administering dexamethasone prior to intrathecal morphine would have a therapeutic benefit, as has been observed when it is dosed prior to morphine delivered epidurally.

In the obstetric population, the timing of dexamethasone administration has importance beyond its potential effects on PONV because the risks and benefits of fetal exposure must be considered. Although there is no evidence to suggest that a single dose of maternal antenatal steroids an hour prior to delivery is associated with adverse outcomes in mother or child,[13,14] a dose-related decline in hypothalamic-pituitary-adrenal axis activity has been noted up to four months after birth in babies whose mothers received antenatal glucocorticoids[15] Therefore, a strong level of evidence supporting the use of dexamethasone for PONV prophylaxis would be necessary to justify its routine use in this population. The upper bound of the 95% CI for the difference between the groups in this study was an absolute 19% reduction in PONV. While it could be debated that this effect size, if replicated in a large effectiveness trial, could shift the risk-benefit considerations towards advocating the use of dexamethasone, the low probability that this boundary represents the true effect does not alter our conclusion that the intervention is not supported by present evidence.

Only one study to date (an RCT by Cardoso *et al.* in 2013)[7] supports the use of dexamethasone for PONV prophylaxis in this setting. In that study, 70 women undergoing Cesarean delivery under spinal anesthesia with 0.06 mg of intrathecal morphine were randomized to receive either dexamethasone (10 mg) or placebo intravenously prior to surgical incision. The data leaned towards a decreased incidence of nausea and vomiting in the dexamethasone group, but statistical significance was not established at any discrete time point. An evaluation of cumulative PONV led to the conclusion that dexamethasone may have benefit, but this was derived from a secondary analysis that double-counted patients reporting PONV at multiple time points. Our present study was powered to detect a smaller benefit of dexamethasone and applies a rigorous statistical approach. While we cannot dismiss that differences in dose timing and morphine dose might underlie the divergent results between the present study and that of Cardoso *et al.*,[7] we believe that our results strongly shift the weight of evidence towards the conclusion that dexamethasone is ineffective for PONV prophylaxis in the setting of intrathecal morphine.

It is possible that, in the setting of intrathecal morphine, dexamethasone is ineffective as a single agent but may act synergistically with other antiemetics. Wu *et al*. found no statistically significant decrease in PONV relative to placebo when dexamethasone was administered as a single agent.[6] There was, however, a statistically significant difference when dexamethasone was administered along with droperidol. This difference was greater than droperidol administered alone, although the study was not powered to find a significant difference between these two groups.

It is important to note that our study reported an IONV and PONV incidence at the upper limit of published incidence estimates. Nevertheless, no significant differences in incidence of either IONV or PONV were noted between study group and placebo group.

Though not a significant difference, the incidence of IONV was higher in the dexamethasone group than the placebo group (43.6% *vs* 26.4%, respectively; $P = 0.06$). Therefore, the negative results observed in PONV differences could be a result of higher than expected IONV in the treatment group. Given the pragmatic design of our study and lack of standardization of intraoperative technique and other intraoperative management, our high incidence of IONV may be related to bupivacaine dosage, management of intraoperative hypotension, administration of uterotonics, fluid management, and dosing of ondansetron. Exteriorization of the uterus was not a recorded variable during this study. Despite this lack of standardization, no significant differences in these characteristics were noted between study group and placebo.

Our study hypotheses did not include an effect of dexamethasone on IONV, and we cannot assess the degree to which the relationship between IONV and PONV represents a common treatment effect, or whether it derives from other non-treatment factors leading to

asymmetry in the risk of nausea and vomiting complications. Given this important limitation, our results should not be interpreted to suggest that the administration of dexamethasone has emetogenic effects contributing to this higher incidence of IONV. Prior studies looking at the use of dexamethasone for PONV prevention during Cesarean delivery do not report the incidence of IONV.[5–7]

Our high incidence of PONV may be a result of our data collection, as we asked patients to report nausea at any time prior to the time of data collection, not just at the time of the visit. This may result in more frequent reporting of nausea than other collection methods. It may also be a result of the observed incidence of IONV.

Importantly, all participants in our study who experienced IONV reported PONV. The observed incidence of PONV (80.0–84.9%) decreases the likelihood that the sample size is responsible for a type II error, given that the study was powered to detect a difference in PONV at an estimated incidence of 53%.

A secondary aim of this study was to assess whether dexamethasone administered prior to intrathecal morphine can reduce pain, as assessed by NRS pain scores and total opioid analgesic use. Nevertheless, this study was not powered to detect a difference in measures of postoperative pain. Indeed, we did not show a significant reduction in NRS pain scores or total opioid consumption at any time point. Nevertheless, the results did display numerically reduced pain scores in the dexamethasone group, occurring at all time points during the first 24 hr. Furthermore, as the study was not powered to assess this secondary outcome, the possibility of a type II error cannot be excluded. This result is noteworthy because all three earlier RCTs identified similar results in at least some of their study time points.[5–7] Future studies adequately powered to assess pain as a primary outcome are required to elucidate whether there is a role for dexamethasone in this population. As the results from the existing trials do not appear to implicate that dose timing is a significant factor, concerns regarding fetal exposure to steroids may be less relevant in assessing this domain.

A limitation of the generalizability of this study is inter-practitioner variation in the dose of intrathecal morphine administered in this setting. The 0.2 mg dose of morphine was chosen as this dose was used in the original two RCTs.[5,6] As a lower dose of morphine has been shown to result in a lower incidence of PONV,[16] it is now common practice for obstetric anesthesiologists to administer less than the 0.2 mg used in our study. The higher dose of intrathecal morphine can be considered a weakness of this study. We cannot definitively conclude that the results of our study are generalizable to lower doses of intrathecal morphine, although there is no specific basis to suggest otherwise.

Dexamethasone was given at a dose of 8 mg. This dose was chosen because it is the most common dose used in RCTs included in the two meta-analyses.[4,8] Two of the three prior intrathecal morphine RCTs used the 8 μg dose and the third used 10 mg. As a lower dose of intravenous dexamethasone is being incorporated into practice, these results may not be generalizable to the lower dose. Dexamethasone was administered as an infusion and this administration route has not been reported to be associated with side effects such as pruritis and perineal itching.[10] Nevertheless, patients were not specifically asked if they experienced those side effects so it is possible that this study includes errors due to participant unblinding.

In conclusion, this randomized double-blind placebo-controlled trial does not support the use of intravenous dexamethasone prior to intrathecal morphine for PONV prophylaxis in Cesarean delivery. There is, however, a suggestion from the results of this and other studies that dexamethasone may improve pain outcomes in the first 24 hr postpartum. This possibility remains inadequately addressed, and calls for future appropriately powered RCTs to assess pain outcomes as a primary measure.

Author contributions All authors contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article.

Conflicts of interest None.

Funding statement This study was funded by departmental support from the Department of Anesthesiology of Weill Cornell Medicine. There are no additional commercial or non-commercial affiliations, associations, or sources of funding to disclose.

Editorial responsibility This submission was handled by Dr. Hilary P. Grocott, Editor-in-Chief, *Canadian Journal of Anesthesia.*

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