Obstetrical and Pediatric Anesthesia

Oral sodium citrate increases nausea amongst elective Cesarean delivery patients

[Le citrate de sodium oral augmente les nausées pendant la césarienne réglée]

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Purpose: Historically, aspiration of gastric contents with subsequent pneumonia was a major cause of anesthesia-related maternal mortality. Before elective Cesarean delivery, gastric fluid can be neutralized with histamine-2 blockers or with oral sodium citrate. Although sodium citrate is commonly used, many patients dislike its taste. We designed this study to determine whether or not patients are more likely to experience nausea during Cesarean delivery when sodium citrate is administered preoperatively.

Methods: One hundred and twenty-three healthy women carrying a singleton fetus and scheduled for elective Cesarean delivery under spinal anesthesia were randomized to receive either sodium citrate 30 mL *po* and saline 2 mL *iv* (sodium citrate group), or water 30 mL *po* and famotidine 20 mg *iv* (famotidine group). Spinal anesthesia consisted of 1.6 mL of 0.75% bupivacaine (12 mg), fentanyl 20 μg, and preservative-free morphine 200 μg. Patients were asked to rate the degree of nausea present at one and five minutes after spinal placement, at the time of uterine exteriorization, and upon arrival to the recovery room. At each time point, the patient's systolic blood pressure and heart rate were recorded.

Results: At all recorded intervals, the average degree of nausea was greater in the sodium citrate group compared to the famotidine group. The frequency of nausea was also greater in the sodium citrate group compared with the famotidine group (37% *vs* 14% respectively, $P < 0.05$) five minutes after establishment of spinal anesthesia. The frequencies of nausea were not significantly different between groups at other time periods.

Conclusion: Nausea is more common during Cesarean delivery in women who receive oral sodium citrate rather than *iv* famotidine for aspiration prophylaxis.

***Objectif** : Historiquement, l'aspiration du contenu gastrique, et une pneumonie subséquente, a été la cause majeure de mortalité maternelle reliée à l'anesthésie. Avant la césarienne réglée, le liquide stomacal peut être neutralisé avec des inhibiteurs H_2 de l'histamine ou du citrate de sodium oral. Le citrate de sodium est couramment utilisé, mais de nombreuses patientes n'en aiment le goût. Nous voulions vérifier si les patientes avaient plus de nausées, ou non, pendant la césarienne précédée de l'administration de citrate de sodium.*

***Méthode** : Cent vingt-trois femmes saines porteuses d'un seul enfant et devant subir une césarienne réglée sous rachianesthésie ont été réparties au hasard et ont reçu, soit 30 mL po de citrate de sodium et 2 mL de solution salée iv, soit 30 mL d'eau po et 20 mg de famotidine iv. La rachianesthésie consistait en 1,6 mL de bupivacaïne à 0,75 % (12 mg), 20 μg de fentanyl et 200 μg de morphine sans agent de conservation. On a demandé aux patientes de préciser le degré de nausées à une et à cinq minutes après l'administration de l'anesthésie, au moment de l'extériorisation utérine et à l'arrivée en salle de réveil. Lors de chaque mesure, la tension artérielle systolique et la fréquence cardiaque étaient enregistrées.*

***Résultats** : Le degré moyen des nausées a été plus élevé avec le citrate de sodium comparé au famotidine à chaque intervalle de mesure. La fréquence des nausées a aussi été plus grande avec le citrate de sodium qu'avec le famotidine (37 % vs 14 % respectivement, $P < 0,05$) cinq minutes après l'administration de la rachianesthésie. La fréquence des nausées n'a pas été significativement différente entre les groupes aux autres temps de mesure.*

***Conclusion** : Les nausées sont plus fréquentes pendant la césarienne chez les femmes qui reçoivent du citrate de sodium oral plutôt que du famotidine iv pour prévenir l'aspiration.*

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HISTORICALLY, aspiration of regurgitated gastric contents with subsequent pneumonia was a major cause of anesthesia-related maternal mortality. Several practices have been adopted to minimize this risk: a) the use of regional anesthesia whenever possible; b) preoperative fasting and neutralization of gastric acidity; and c) endotracheal intubation when general anesthesia is required. These practice changes have greatly reduced the incidence of life-threatening aspiration pneumonia. One hospital reported a total of eight aspirations in 12,380 general anesthetic Cesarean deliveries (0.064% incidence) with no maternal or neonatal mortality.[1] The 2000-2002 Confidential Enquiry into Maternal Death reported no fatal aspirations in 340,000 Cesareans performed under regional anesthesia and one aspiration death in 85,000 general anesthetics for Cesarean delivery.[2] Because aspiration is now such a rare cause of mortality during Cesarean delivery under regional anesthesia, we decided to examine potentially unpleasant side effects of oral sodium citrate prophylaxis.

Before elective Cesarean delivery, gastric fluid pH increases comparably with either famotidine or oral sodium citrate.[3–5] Although sodium citrate is commonly used, many patients dislike its taste and some patients complain of nausea.[6,7]

We hypothesized that women having elective Cesarean delivery under spinal anesthesia would have a higher incidence of nausea when receiving sodium citrate rather than water and famotidine immediately prior to surgery. We designed a randomized trial to test this hypothesis.

Methods

This study was approved by the Institutional Review Board of Weill Medical College of Cornell University. After signing a written consent form to participate in our study, 123 healthy women carrying a singleton fetus and scheduled for elective Cesarean delivery under spinal anesthesia were randomized to receive either sodium citrate 30 mL *po* and saline 2 mL *iv* (sodium citrate group), or water 30 mL *po* and famotidine 20 mg *iv* (control group). The principal investigator's secretary prepared sealed opaque envelopes with sequential assignments by flipping coins. Each patient's envelope was opened after randomization. Inclusion criteria were term gestation and a period of fasting greater than eight hours. Excluded were patients who routinely used antacids or antiemetics during pregnancy, and those with nausea in the 24 hr prior to elective Cesarean delivery. Intravenous solutions were given 90 min and oral solutions 15 min prior to spinal placement. Spinal anesthesia consisted of 1.6 mL of 0.75% bupivacaine (12 mg), fentanyl 20 μg, and preservative-free morphine 200 μg. Immediately before the administration of the oral solution, each patient had her baseline systolic blood pressure and pulse measured, and was asked to report nausea on a scale of 1 to 5 (1 = no nausea, 2 = mild nausea, 3 = moderate nausea, 4 = severe nausea, 5 = vomiting) to an observer blinded to the randomization sequence. Immediately after swallowing the study medication, patients rated the taste of the oral solution on a scale of 1 to 5 (1 = very pleasant, 2 = pleasant, 3 = neutral, 4 = unpleasant, 5 = very unpleasant).

Spinal anesthesia was introduced in the sitting position, and the patient was immediately positioned supine with left uterine displacement. To control for systemic hypotension as a potential confounding variable, an infusion of ephedrine 5 $mg \cdot min^{-1}$ and phenylephrine 20 $\mu g \cdot min^{-1}$ was initiated immediately upon positioning the patient supine. Blood pressure was measured at one-minute intervals, and the drug infusion was then discontinued either ten minutes after spinal placement, or once systolic blood pressure exceeded the patient's baseline value. Thereafter, additional boluses of ephedrine 5 mg and phenylephrine 20 μg were given only as required to maintain systolic blood pressure at baseline values.

The degree of nausea was assessed using the same scale at four time points: one minute after spinal placement, five minutes after spinal placement, at the time of uterine exteriorization (the uterus was exteriorized in all study patients), and once the patient reached the recovery room. At each interval, the patient's systolic blood pressure and heart rate were recorded. Hypotension was defined as systolic blood pressure ≤ 100 mmHg. Dolasetron 12.5 mg *iv* was given if needed for persistent nausea and vomiting after exteriorization of the uterus.

Statistical analysis

With an expected incidence of intraoperative nausea of 33% and an expected reduction in that rate by 10% by the omission of sodium citrate, a necessary sample size of 55 patients per group was required to achieve 50% statistical power with a 5% α.[8] All patients with nausea scores of 2, 3, 4, or 5 were considered to have nausea. Differences in the incidence of nausea and vomiting were compared in two ways. First, mean nausea scores were compared at each time point, using Student's t test for significance. Recognizing the potential confounding influence of hypotension, average systolic blood pressures were also compared at each time point. Second, the Pearson Chi-square test was used

TABLE I Demographic data

	Sodium citrate (n = 60)	*Control (n = 63)*
Age (yr)	35.2 ± 5.6	34.1 ± 4.6
BMI ($kg \cdot m^{-2}$)	28.6 ± 9.3	30.5 ± 10.6
Multiparous (*n*)	40 (67%)	41 (65%)
Baseline systolic BP (mmHg)	120 ± 14	116 ± 11
Heart rate ($beats \cdot min^{-1}$)	82 ± 11	81 ± 12
Nausea at baseline (*n*)	7 (12%)	6 (10%)

BMI = body mass index; BP = blood pressure; age, BMI, systolic BP and heart rate are summarized as mean ± SD. Nausea = 2–5 on a scale of 1–5, with 1 being no nausea and 5 being vomiting.

TABLE II Occurrence of nausea and hypotension

	Sodium citrate	*Control*	*P-value*
1 min after spinal			
Nausea	4/60 (7%)	2/63 (3%)	0.43
Hypotension	4/59 (7%)	4/61 (7%)	1
5 min after spinal			
Nausea	22/60 (37%)	9/63 (14%)	0.006
Hypotension	13/60 (22%)	11/63 (17%)	0.65
Uterine exteriorization			
Nausea	14/53 (26%)	7/52 (13%)	0.14
Hypotension	1/53 (2%)	2/53 (4%)	1
Recovery room			
Nausea	17/58 (29%)	15/62 (24%)	0.54
Hypotension	5/60 (8%)	9/63 (14%)	0.39

Nausea = 2–5 on a scale of 1–5, with 1 being no nausea and 5 being vomiting. Hypotension = systolic blood pressure ≤ 100. Compared with Pearson Chi-square test.

to compare the incidence of nausea at each time point. Again, the incidence of hypotension was compared at each time point. Finally, logistic regression was used to adjust for the effects of hypotension, to determine the odds ratio of developing nausea with sodium citrate at each time point. Two-tailed probability values were used throughout. Calculations were performed using SPSS 12.0.1 for Windows (Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

Results

A total of 190 patients were screened for participation in the study, but only 125 were enrolled. Thirty-five patients declined to participate, 13 met criteria for exclusion, and 17 were enrolled but not studied due to logistical problems such as last-minute scheduling changes and unavailability of the blinded observer. Demographic data (age, body-mass index, parity, baseline systolic blood pressure, baseline heart rate, and the incidence of nausea at baseline) did not differ between the sodium citrate and famotidine groups (Table I). The taste of the oral solution was rated as

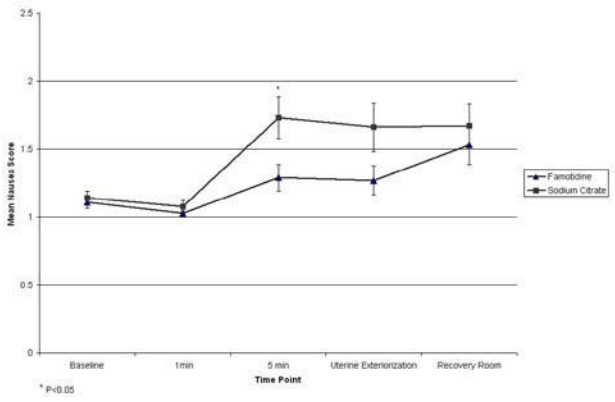

FIGURE 1 Average degree of nausea over time.

either unpleasant or very unpleasant by two-thirds of the patients receiving *po* sodium citrate, but by none of the patients in the famotidine group.

Within the first minute of completing the spinal anesthetic, the average degree of nausea was similar in the sodium citrate and famotidine groups (1.08 and 1.03, respectively), while the frequencies of nausea were low, but similar (7% and 3%, respectively). However, within five minutes of block establishment, the average degree of nausea was greater in the sodium citrate group compared to the famotidine group (1.73 and 1.29, respectively, $P = 0.01$). Also, the presence of any degree of nausea was significantly more common in the sodium citrate group (37% *vs* 14%, $P = 0.006$). During uterine exteriorization, twice as many patients experienced nausea in the sodium citrate group as compared to the famotidine group (26% *vs* 13%, respectively) although the numerical percentage difference did not achieve statistical significance ($P = 0.14$). By the time patients arrived in the recovery room, the degrees and frequencies of nausea experienced by patients were similar in the two groups. Summary data are presented in Figure 1 and Table II.

Despite the preemptive use of vasoactive medications to prevent hypotension, some patients experienced a decrease in systolic blood pressure. Hypotension occurred with similar frequencies in the two groups (Table II, Figure 2). Logistic regression, adjusting for the effects of hypotension, confirmed that sodium citrate had a highly significant effect on the odds of developing nausea (odds ratio = 3.65) at five minutes after spinal placement ($P = 0.006$). By numbers needed-to-treat analysis, this translates into

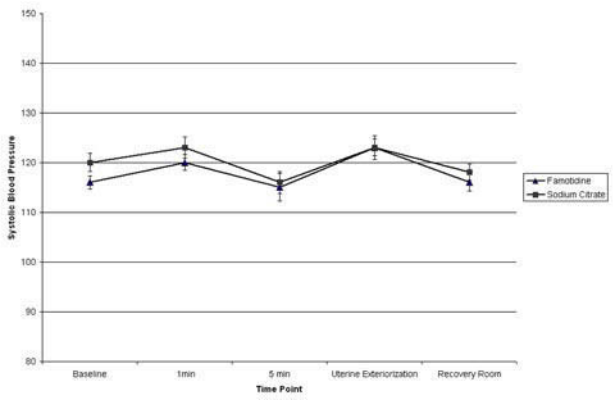

FIGURE 2 Average systolic blood pressure over time.

TABLE III Odds ratio for developing nausea with sodium citrate

	Odds ratio	*P-value*	*Numbers needed to treat (confidence interval)*
1 min after spinal	2.179	0.38	
5 min after spinal	3.650	0.006	4 (2, 50)
Uterine exteriorization	2.308	0.10	
Recovery room	1.299	0.52	

Determined using logistic regression to adjust for hypotension (systolic blood pressure ≤ 100).

one case of nausea avoided for every four patients (confidence interval 2–50) not given oral sodium citrate prior to elective Cesarean delivery under spinal anesthesia (Table III).

Discussion

Aspiration pneumonia during elective Cesarean delivery under regional anesthesia is now an exceedingly rare cause of maternal mortality in the developed world. Patients for elective Cesarean delivery have fasted preoperatively. Additionally, recent work suggests that non-labouring patients do not have delayed gastric emptying at term pregnancy.[9] Therefore, gastric volume in patients undergoing scheduled Cesarean delivery is expected to be on average lower than in those undergoing unplanned Cesarean delivery during the course of labour. General anesthesia needs to be induced in 2 to 2.9% of patients scheduled for spinal anesthesia for Cesarean delivery.[10,11] Aspiration occurs in only 0.064% of general anesthetic Cesarean patients.[1] No cases of fatal aspiration were reported in the United States from 1979-1990 or in the United Kingdom from 2000-2002.[2,12] Despite the low aspiration risk implied by these numbers, patients scheduled for elective Cesarean delivery under spinal or epidural anesthesia are frequently asked to drink oral sodium citrate (e.g., Bicitra®) preoperatively.

While our study is the first to document a significant increase in the incidence of nausea with oral sodium citrate, it has long been known that these solutions are considered highly unpleasant by most patients. Several products have been marketed as better-tasting sodium citrate solutions; however, none has succeeded in capturing the market, and no product, in our opinion, tastes better than Bicitra®.

Hypotension is a strong trigger for nausea during Cesarean delivery. We administered a mixture of ephedrine and phenylephrine preemptively to prevent and treat hypotension in order to minimize the effect of systemic hypotension on the results. The observed incidence of hypotension (≤ 22% at all time points studied) was lower than that usually reported during spinal anesthesia for Cesarean delivery (55–85%).[13,14] We believe this is why the incidence of nausea in the sodium-citrate-treated patients (7–37%) was lower than the incidence reported in other studies (63–76%).[6,7]

The results of our study differ from those of the only other randomized study on this subject. Palmer *et al.* found that oral Bicitra® did not affect the incidence of nausea during Cesarean delivery.[8] However, Palmer *et al.* studied fewer patients, and included patients receiving epidural, as well as spinal anesthesia. In addition, hypotension was not controlled as aggressively as was the case in the current investigation. It is also possible that the famotidine suppressed nausea in our study.

Histamine-2 blockers have been used extensively before Cesarean delivery.[3,4,15] In one randomized trial, famotidine 20 mg given to mothers one hour before Cesarean delivery did not affect neonatal gastric acidity, liver function tests, or Apgar scores. The umbilical venous: maternal venous ratio was 0.64 ± 0.13.[16] Histamine-2 blockers, including famotidine, are frequently used in infants to treat gastroesophageal reflux or prevent stress ulceration.[17,18]

In conclusion, nausea during Cesarean delivery is more frequent in women receiving oral sodium citrate rather than *iv* famotidine. Therefore, we recommend the preoperative use of a histamine-2 blocker rather than oral sodium citrate to neutralize maternal gastric acidity in parturients scheduled for elective Cesarean delivery under spinal anesthesia.

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