The effect of gestational diabetes mellitus on sufentanil consumption after cesarean section: A prospective cohort study

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Research article

Keywords: Gestational diabetes mellitus; postoperative analgesia; cesarean section

Posted Date: April 26th, 2019

DOI: https://doi.org/10.21203/rs.2.9274/v1

Version of Record: A version of this preprint was published on January 9th, 2020. See the published version at https://doi.org/10.1186/s12871-019-0925-1.

Abstract

Background: Previous studies have shown that patients with long-term diabetes require more opioids after surgery than patients without diabetes. Gestational diabetes mellitus (GDM) normally only lasts for a brief period; nevertheless, its effect on sufentanil consumption after cesarean section is unknown. Methods: This prospective cohort study included two groups: a GDM group (n=32) and a matched non-GDM (NGDM) group (n=32). All patients underwent routine combined spinal-epidural anesthesia for cesarean delivery. Sufentanil consumption through an intravenous patient-controlled analgesia (PCA) pump, the frequency of PCA requests, and visual analog scale (VAS) scores 6 and 24 hours after surgery were compared between groups. Results: Sufentanil consumption (μg) 6 hours after surgery was higher in the GDM group than in the NGDM group (24.0±6.6 vs 20.1±5.7, P=0.023). PCA was used more frequently 6 and 24 hours after surgery by the GDM group than by the NGDM group (1[0-2] vs 0[0-1], P=0.001; 6[4-8] vs 3[1-5], P=0.001, respectively). The VAS score during activity 24 hours after surgery was higher in the GDM group than in the NGDM group (5[5-6] vs 5[4-5], respectively, P=0.03). Conclusion: Pregnant women with GDM require more opioids during the immediate postoperative period after cesarean section than those without GDM.

Introduction

Gestational diabetes mellitus (GDM) refers to varying degrees of high blood glucose caused by an impaired glucose tolerance and diabetes detected or diagnosed during pregnancy. GDM is characterized by elevated fasting blood glucose and impaired glucose tolerance during pregnancy. In most cases, GDM resolves 1 to 2 months after delivery ("transient diabetes"). GDM is one of the most common pregnancy complications, with a prevalence of approximately 3% to 7%[1,2,3].

Karci et al. showed that the analgesic effect of morphine is negatively affected by high blood glucose in patients scheduled for elective total abdominal hysterectomy[4]. Patients with diabetes require more opioids than patients without diabetes according to postoperative intravenous patient-controlled analgesia (PCA) data. Glycated hemoglobin (HbA1c) is a highly reliable indicator of glycemic control over the previous 8 to 12 weeks[5]. Kim et al. conducted a prospective observational study and found that perioperative HbA1c was positively correlated with postoperative opioid (fentanyl) consumption among patients with diabetes undergoing open nephrectomy[6]. However, the mechanism that underlies this relationship is unknown. Chronic high blood glucose might affect opioid receptors, thereby altering the pharmacokinetics and pharmacodynamics of opioids[7]. Alternatively, chronic high blood glucose might affect a patient's metabolism[8] or neurotransmitters[9].

The patients included in previous studies had been diagnosed with diabetes for at least 60 weeks;[6] however, the course of gestational diabetes is usually briefer. As a result, whether gestational diabetes has the same effects as those described above is unclear. Therefore, we conducted this prospective observational cohort study to investigate the effect of gestational diabetes on sufentanil consumption during the immediate postoperative period after cesarean section. We hypothesized that pregnant women with GDM require more opioids during the immediate postoperative period after cesarean section than those without GDM.

Methods

Participants

The Ethics Committee of the Obstetrics and Gynecology Hospital, Fudan University approved this prospective, observational cohort study, and it was registered at the Clinical Trials Registry (http://www.chictr.org.cn/; Registration No. ChiCTR1800016014). This study was conducted between June 2018 and October 2018 at the Obstetrics and Gynecology Hospital, Fudan University. Inclusion criterion: pregnant women with a single fetus scheduled to undergo cesarean section under combined spinal-epidural anesthesia. Exclusion criteria: a history of opioid allergies, a history of opioid use within the previous week, contraindications for spinal anesthesia, pre-GDM and other pregnancy complications (e.g., gestational hypertension, pregnancy complicated with hypothyroidism, and preeclampsia). Then, pregnant women who met the above criteria with GDM were included in the GDM group. Whenever one pregnant women with GDM was included, followings without GDM who first matched with regard to height, weight, and parity was included in the NGDM group (Figure 1). Patients signed an informed consent document before the study.

Procedure

On the morning of cesarean section, blood was drawn to measure maternal glucose and HbA1c. Maternal age, height, weight, gestational age, and parity data were recorded. Moreover, the blood glucose management methods of the GDM group were recorded such as diet restrictions, oral medications (and doses), and insulin injections (and doses).

No medication was given before the operation. In the operating room, an 18-gauge needle was used to puncture a vein in the right upper arm, and an indwelling catheter was placed. Blood pressure, electrocardiograms (ECGs), heart rate, and pulse oximetry were routinely monitored noninvasively. Baseline values were recorded. At the beginning of anesthesia, 6% hydroxyethyl starch was infused at 20 mL/min until delivery. Then, the infusion speed was adjusted according to the maternal circulation state until the total amount of 500 ml hydroxyethyl starch was completed and replaced with ringer lactate solution. A combined spinal-epidural anesthesia was performed with patients in the left lateral position at the L3-4 or L2-3 vertebral interspace. An 18-gauge Tuohy needle was placed in the epidural space using the loss of resistance to saline; then, a 25-gauge Whitacre spinal needle was inserted through the Tuohy needle until the dura mater was punctured. Next, 8~10 mg bupivacaine was diluted with cerebrospinal fluid to 3 ml for intrathecal injection; then, an epidural catheter (3-4 cm) was immediately placed. The patient was placed in the supine position, and the operating table was tilted to the left. During the first 10 minutes after spinal anesthesia administration, a needle was used to test the sensory block level every 2 minutes. The operation began once the block level reached T6. Patients who did not achieve this level were excluded from the study, and 1.5% lidocaine was injected epidurally until successful anesthesia was achieved. During the operation, the patient received continuous supplementary oxygen through a mask at 5 L/min. If hypotension occurred (i.e., systolic blood pressure

<90 mm Hg or a decrease by >20% from baseline), then 40 μg of phenylephrine was given intravenously (iv) and repeated as needed; furthermore, the infusion rate of hydroxyethyl starch was increased. If sinus bradycardia occurred (heart rate <50 bpm), then 0.2 mg of atropine was given iv, which was repeated as needed. If pain occurred after delivery but during the operation, it was treated with intravenous analgesics.

After the infant was delivered and the umbilical cord was clamped, 50 mg of flurbiprofen and 4 mg of ondansetron were administered intravenously. At the end of the operation, 5 μg of sufentanil (diluted in saline to 5 mL) was given via epidural injection, and the epidural catheter was removed. The operative time and blood loss were recorded.

After the operation, the patient was moved to the postanesthesia care unit (PACU). Once the patient's blood pressure and heart rate were normal and the anesthesia level was T6 or below, an intravenous analgesia pump (Aipeng, Nantong Apon Medical Devices Co., Ltd.) was connected, and the patient was instructed with regard to its proper use. Analgesics given via patient-controlled intravenous analgesia (PCIA) included sufentanil 150 μg and ondansetron 4 mg diluted in saline to 150 mL. The background dose was 3 mL/h, with a bolus dose of 3 mL and a lock-out time of 15 minutes. The anesthesia nurse involved in the study recorded the use of the postoperative analgesia pump (sufentanil consumption and number of PCA compressions [reflecting maternal needs]) as well as adverse reactions such as nausea, vomiting, and itching. Patients with nausea and vomiting were given ondansetron (4 mg, iv), which was repeated as needed. Moreover, a visual analog scale (VAS, 0 cm ~10 cm) was used to assess pain during rest and activity 6 and 24 hours after the operation. In addition, patient satisfaction with the postoperative analgesia was evaluated as 1 (very dissatisfied), 2 (dissatisfied), 3 (neither dissatisfied nor satisfied), 4 (satisfied), or 5 (very satisfied). Patients were excluded from this study if general anesthesia or intraoperative intravenous opioids were used, if they underwent hysterectomy due to bleeding or other reasons, if they discontinued the analgesia pump for any reason, or if they asked to be withdrawn from the study early.

Statistical analysis

The primary endpoint was sufentanil consumption 6 hours after the operation. The secondary endpoints included sufentanil consumption 24 hours after the operation, the frequency of PCA press 6 and 24 hours after the operation, the VAS score, adverse reactions during postoperative analgesia administration, and patient satisfaction with postoperative analgesia. The Kolmogorov-Smirnov test was performed to determine whether the data displayed a normal distribution. Normally distributed measurement data were expressed as means±standard deviations and analyzed with an independent-samples t-test. Categorical data (e.g., nausea, vomiting, and itching) were analyzed using Fisher's exact test. SPSS v22.0 (SPSS Inc., Chicago IL, USA) was used for all analyses, and $P < 0.05$ was considered as significant. A multivariate covariance analysis was done to eliminate the offset effect of the statistically significant variables between the two groups on the results.

The primary endpoint was sufentanil consumption 6 hours after the operation. We referenced a previous studythat used the same analgesia regimen as that in this study to estimate the necessary sample size[10], knowing that NGDM patients used 15.8 ± 6.3 μg of sufentanil 6 hours after the operation. We determined that the difference between GDM patients and NGDM patients must be at least 20% (4.6 μg) to reach clinical importance. With two-tailed tests, α=0.05 and β=0.2, and at least 29 patients were required for each group. Ultimately, 32 patients were included in each group, allowing for a 10% attrition rate.

Results

All patients (32 in each group) completed this study (Figure 1). Their demographics and intraoperative characteristics are shown in Table 1. Women in the GDM group were older and had an earlier gestational age than those in the NGDM group (P=0.042, 0.004, respectively).

Preoperative laboratory tests showed that fasting blood glucose (mmol/l) was higher in the GDM group than in the NGDM group (4.8±0.2 vs 4.3±0.4, respectively, P<0.001), despite blood glucose management in the GDM group (diet restriction, medication, and insulin). HbA1c was significantly higher in the GDM group than in the NGDM group (5.9±1.8 vs 4.9±0.2, respectively, P=0.003). No significant between-group differences were observed with regard to other indicators.

The analgesic information is shown in Table 2. The GDM group used the analgesia pump more frequently than did the NGDM group 6 and 24 hours after the operation (P<0.005). Sufentanil consumption (ug) 6 hours after the operation was higher in the GDM group than in the NGDM group (24.0±6.6 vs 20.1±5.7, respectively, P=0.023). No significant difference was found with regard to sufentanil consumption between the GDM group (85.4±12.4) and the NGDM group (80.5±13.5) 24 hours after the operation.

The results of a multivariate covariance analysis showed that the sufentanil consumption of the patients in the GDM group was significantly higher than that in the NGDM group after controlling the age of the pregnant women and gestational age (F=5.097, P=0.028). The corrected sufentanil consumptions of the GDM and NGDM groups 6 hours after surgery were 24.2 (95% CIs: 21.7-26.6) and 20.1 (95% CIs: 17.6-22.5), respectively, and the difference in sufentanil consumption between the groups was 4.5(95% CIs: 0.5-7.7)(Table 3).

The VAS scores during rest and activity were assessed 6 and 24 hours after the operation (Table 2). The VAS score during activity 24 hours after the operation was higher for the GDM group than for the NGDM group (5[5-6] vs 5[4-5], P=0.03). No significant between-group differences were found with regard to the pain scores at the 6-hour postoperative rest/activity measurement the 24-hour postoperative rest measurement.

No significant between-group differences were observed in adverse reactions during postoperative analgesia administration or with regard to patient satisfaction with postoperative analgesia (Table 4).

The normal value of HbA1c ranges from 4% to 6%; thus, patients in the GDM group were divided into two subgroups according to whether their HbA1c was greater than 6% (>6% [n=6] vs £6% [n=26]). In the HbA1c £6% group, three patients took medication(s), seven used insulin (12-30 U), and the remaining

patients followed diet restrictions to manage their blood glucose levels. In the HbA1c >6% group, all six patients used insulin to manage their blood glucose. A subgroup analysis showed no significant between-group differences in analgesia needs, sufentanil consumption, or VAS scores.

Discussion

This prospective cohort study showed that pregnant women with GDM require more opioids and exhibit higher sufentanil consumption 6 hours after cesarean section than NGDM patients.

In animal models of diabetes mellitus (DM), high blood glucose has been shown to reduce the effectiveness of opioid receptor agonists[11,12,13]. Studies on relevant mechanisms have shown that high blood glucose is associated with changes in the expression of opioid receptor genes [14,15], the body's metabolism[8], and neurotransmitter levels[9].

Previous studies were conducted in patients with elevated blood glucose (diabetes) for more than 60 weeks[4,6]. By contrast, this study was conducted among pregnant women who were diagnosed with GDM after an abnormal glucose tolerance test at approximately 24 gestational weeks, and women with pre-GDM were excluded. As a result, the course of high blood glucose was only about 100 days or so, which is far briefer than that for a typical patient with diabetes. Nevertheless, this study showed that GDM patients consumed significantly more opioids 6 hours after surgery than NGDM patients. The results were similar to those of previous studies of DM patients[4,6]. This finding is important because few previous studies have focused on GDM, which represents a particular group of hyperglycemic women. Our study shows that GDM still has the same effect on the demand for opioid analgesics despite the brief period of elevated blood glucose.

Kim et al. showed that preoperative HbA1c was positively correlated with the postoperative opioid needs of patients with diabetes[6]. In this study, patients in GDM group were subgrouped based on whether their HbA1c was level >6% given that the normal upper limit of HbA1c level is 6%. However, we found no significant between-group differences in postoperative analgesia consumption, most likely because HbA1c was >6% in only six GDM patients, and the sample size was small. Moreover, GDM patients were excluded from this study if they had other pregnancy complications. For these patients, blood glucose might be more difficult to manage, and we hypothesize that higher fasting blood glucose and HbA1c would result in greater postoperative analgesia needs. Additional studies are needed to validate this hypothesis.

Notably, this study showed a significant between-group difference in the frequency of PCA use, indicating that the GDM group requires significantly more postoperative analgesia than the NGDM group. Moreover, sufentanil consumption was significantly higher in the GDM group than in the NGDM group 6 hours after surgery, with no significant between-group difference in VAS scores. Although sufentanil consumption did not significantly differ between the two groups at 24 hours, the statistically higher VAS and greater PCA use, which reflect maternal needs, suggest an increased opioid requirement in the GDM group that was limited by the "lock-out time" setting of the analgesic pump.

This cohort study matched conditions between the two groups with regard to factors such as weight and height that affect the demand for analgesics. Furthermore, previous studies have shown that contraction pain after a repeat cesarean section is more severe than that after the first[16], so parity was also used as a matching condition. Maternal age and gestational age were not matched. On the one hand, advanced age is a high-risk factor for GDM, and the gestational termination times of the cesarean sections of GDM pregnant women are earlier. On the other hand, no studies have indicated that maternal age or gestational week influence the demand for analgesics. Our results also confirmed these suggestions, and a covariance analysis of the two variables showed that maternal age and gestational age did not affect the results.

This study has some limitations. First, the reference values of oral glucose tolerance test for pregnant women are as follows：Fasting, 5.6 mmol/L; 1-hour postprandial, 10.3 mmol/L; 2-hour postprandial, 8.6 mmol/L; 3-hour postprandial, 6.7 mmol/L. GDM is diagnosed when two or more test values reach or exceed the reference value. The diagnostic criteria were strictly followed, and the patients were instructed to fast for 8 to 12 hours before the test. However, some patients might not have followed this instruction, leading to false-positive results. We did not ask the patients to undergo retesting, although the inclusion of these patients would only reduce between-group differences. Second, we only discussed the analgesia of intravenous sufentanil after cesarean section. However ,many hospitals routinely used intrathecal morphine and intravenous NSAIDs for postoperative analgesia. Whether GDM affects the analgesic effect of these drugs remains to be further studied. In addition, because of the design of the cohort study, a double-blind condition was not possible; however, the researchers responsible for the follow-up assessment were unaware of the study group, and the primary outcome was the objective analgesic pump data; thus, the objectivity of the research results was not affected. Finally, we recorded patient analgesic consumption up to 24 hours after surgery and did not investigate later time points because we usually prescribe 24-hour analgesia administration for routine intravenous analgesia given that patients start eating after 24 hours and can take oral analgesics as needed. Moreover, milk production is usually low (mean: <10 mL/d) during the first 2 days after surgery and then begins to increase. Thus, the short-term use of regular-dose intravenous opioids after delivery results in extremely low drug concentrations in colostrum, with negligible drug intake among infants[17]. And so, 24-hour postoperative intravenous analgesia is safe for nursing infants and helps mothers to resume activities as soon as possible after delivery. Therefore, the results of this study are only applicable to the early postoperative period after cesarean section; whether a difference exists in postoperative long-term analgesia should be explored in future studies.

In summary, pregnant women with GDM require more analgesics and exhibit higher sufentanil consumption during the immediate postoperative period after cesarean section than NGDM patients. Clinicians should focus more on postoperative analgesia management among GDM patients to improve the effectiveness of postoperative analgesia and patient satisfaction.

Declarations

Conflict of interest notification

The authors declare that they have no conflicts of interest.

Funding

This research did not receive any grants from funding agencies in the public, commercial, or nonprofit sectors.

Acknowledgement

We are extremely grateful to Jiangnan Wu MD, at the Department of Clinical Epidemiology, Obstetrics and Gynecology Hospital of Fudan University, for help with statistical analysis of our results.

Authors' contributions

Yang: study design, data collection, data analyses and article drafting. Geng : interpretation of the results and data analyses.Hu: data collection. Huang: study design, interpretation of the results and article drafting. All authors have read, critically revised and accepted the final manuscript.

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Tables

Table 1 Clinical characteristics of the patients

	GDM (n=32)	NGDM (n=32)	P
Age (years)	34.3 ± 0.1	32.1±0.1	0.04
Gestation (weeks)	37.9±1.2	38.8±1.2	0.004
Height (cm)	162.1±3.2	160.9±4.0	0.24
Weight (kg)	69.3±8.5	69.8 ± 8.6	0.48
BMI (kg/m^2)	26.1±3.3	26.9 ± 3.1	0.24
Parity (first/repeat)	14/18	14/18	1
Amount of bleeding (ml)	310±74	315±70	0.34
Duration of surgery (min)	45. 3±4.2	46.5±4.7	0.32
Blood glucose (mmol/l)	4.8±0.2	4.3±0.4	0.0001
HbA1c (%)	5.9±1.9	4.9±0.3	0.003

Data are presented as the mean ± SD or number.

Table 2. Postoperative analgesia

	Number of PCA compression		Sufentanil consumption (ug)		VAS scores (cm)			
					Rest		Movement	
	6 h	24 h	6 h	24 h	6 h	24 h	6 h	24 h
GDM n=32	1[0-2]	6[5-8]	24.0±6.6	85.4±12.4	2[1.5-3]	2[1-2]	2.5[1-3]	5[5-6]
NGDM n=32	0[0-1]*	3[1-5]*	20.1±5.7#	80.5±13.5	2.5[2-3]	2[2-3]	2.5[2-3]	5[4-5]#

Data are presented as the mean ± SD or median [IQR]. *P<0.005 vs GDM; #P<0.05 vs GDM.

Table 3. Covariance analysis of sufentanil consumption 6 hours after surgery between two groups

Source	Sum of Squares (Class III)	Degrees of Freedom	Square of Average	F-value	P-value
Modified model	261.558	3	87.186	1.998	0.124
Intercept	31.749	1	31.749	0.728	0.397
Age	38.968	1	38.968	0.893	0.348
Gestational week	0.216	1	0.216	0.005	0.944
Group	222.408	1	222.408	5.097	0.028
Error	2618.176	60	43.636		

Table 4. Comparison of adverse reactions and patient satisfaction between two groups

	GDM (n=32)	NGDM (n=32)
Nausea	5(16)	4(13)
Vomiting	1(3)	0(0)
Pruritus	3(9)	1(3)
Satisfaction (1/2/3/4/5)	0/0/3/27/2	0/1/1/29/1

Data are number (%)

Figures

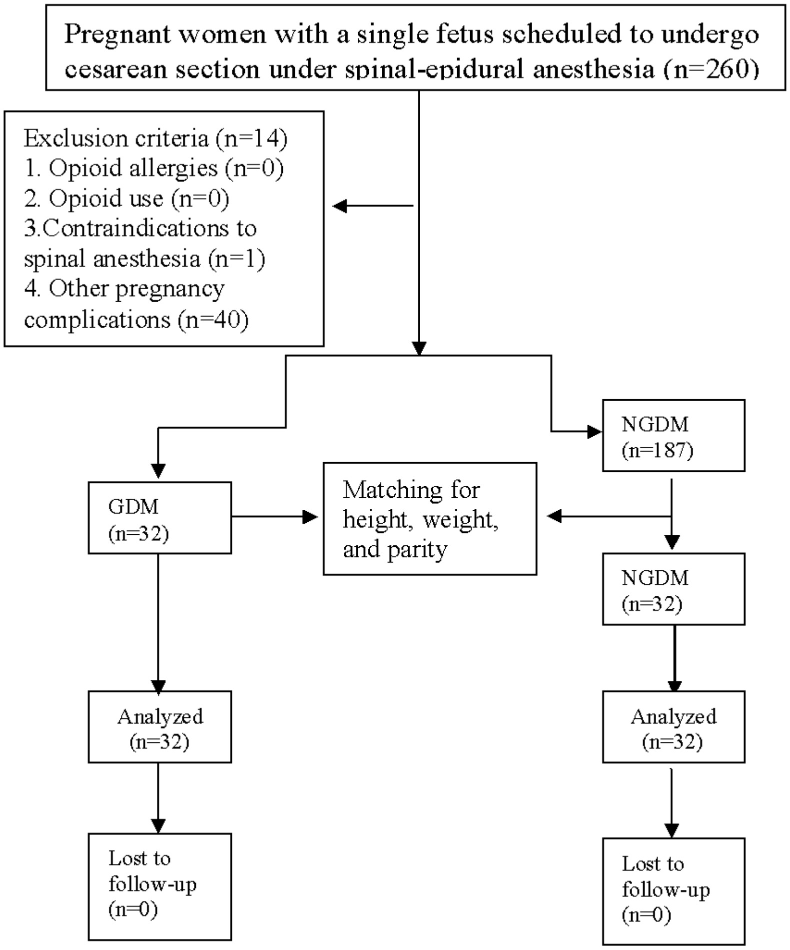
Pregnant women with a single fetus scheduled to undergo cesarean section under spinal-epidural anesthesia (n=260)
Exclusion criteria (n=14)
1. Opioid allergies (n=0)
2. Opioid use (n=0)
3.Contraindications to spinal anesthesia (n=1)
4. Other pregnancy complications (n=40)
NGDM (n=187)
GDM (n=32)
Matching for height, weight, and parity
NGDM (n=32)
Analyzed (n=32)
Analyzed (n=32)
Lost to follow-up (n=0)
Lost to follow-up (n=0)

Figure 1