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Original Article

A Comparison of the Effects of Fentanyl and Remifentanil on Nausea, Vomiting, and Pain after Cesarean Section

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Abstract

Background: The effects of different opioids on postoperative nausea and vomiting (PONV) and pain have not been conclusively determined. The aim of this study was to compare the effects of fentanyl, remifentanil or fentanyl plus morphine on the incidence of PONV and pain in women subjected to cesarean section under general anesthesia.

Methods: The study was a randomized clinical trial recruiting 96 parturients with American Society of Anesthesiologists (ASA) physical status I and II. They scheduled for cesarean section under general anesthesia using sodium thiopental, succynylcholine, and isoflurane O2/N2O 50/50 mixture. After clamping the umbilical cord, the patients were given fentanyl (2 µg/kg/h), remifentanil (0.05 µg/kg/h), or fentanyl (2 µg/kg) pulse morphine (0.1 mg/kg) intravenously. Visual analog scale for pain and nausea, frequency of PONV, meperidine and metoclopramide consumption were evaluated at recovery, and 4, 8, 12 and 24 hours after the surgery.

Results: There was no significant difference between the three groups in terms of frequency of nausea, vomiting, and mean nausea and pain scores at any time points. None of the patients required the administration of metoclopramide. However, the mean VAS for pain in remifentanil-treated group was insignificantly more than that in fentanyl- or fentanyl plus morphine-treated group at recovery or 4 hours after the surgery. The mean mepridine consumption in remifentanil-treated group was significantly (P=0.001) more than that in fentanyl- or fentanyl plus morphine-treated group in 24 hours after the surgery respectively. There was no significant difference in hemodynamic parameters of the three groups in all measurements after the surgery.

Conclusion: The findings of this study showed that early postoperative analgesia was better with fentanyl, and postoperative meperidine consumption was significantly less with fentanyl than with remifentanil or combined fentayl and morphine.
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Keywords ● Fentanyl ● remifentanil ● postoperative nausea and vomiting ● cesarean section

Introduction

Nausea and vomiting in the postoperative period occur in 20% to 30% of patients, and together are the second most common complaints reported.[1] Although a number of studies have shown several risk factors for postoperative nausea and vomiting (PONV) following different type of procedures, the incidence of PONV remains high.[2-4] Postoperative nausea and vomiting contributes to patients discomfort and unanticipated hospital admissions.[5,6] Short-acting opioids have often been incriminated as a major cause of postoperative nausea and vomiting in ambulatory surgical patients. In addition, the amount of opioid administered seems to affect the incidence of PONV.[7,8] It is not known whether nausea or vomiting bears simple relationship to plasma opioid concentration. Although opioids stimulate the chemoreceptor trigger zone, the classic animal studies of Borison and Wang suggest that high dose may also depress the vomiting center.[9] In parturients, the pain of labor may delay gastric emptying and promote emesis. These changes may be caused by the effects of placentally derived gastrin.[1,10]

Systemic opioids are widely used to provide postoperative pain relief, but analgesia is rarely maintained for more than a few hours, especially with short-acting opioids such as fentanyl and remifentanil.[1,3] Remifentanil has been recently introduced into anesthetic practice. It is cleared very rapidly by circulating tissue esterases, and has been associated with PONV in previous studies.[5] In an early study in volunteers, a high incidence of nausea was observed and persisted for hours in some of the subjects.[11] Wether the short half-life of remifentanil, in comparison with longer-acting opioids, influences the incidence or time course of PONV in parturients undergoing cesarean section is unknown. Therefore, the present study was designed to examine the effects fentanyl and remifentanil on the incidence of PONV and pain following cesarean section in term pregnancies.

Materials and Methods

This is a prospective, randomized, double blind study performed at Alzahra General Hospital, Isfahan, Iran from 2005 to 2007. The study was approved by the Hospital Ethics Committee, and written informed consents were obtained from all participants. The study recruited 96 parturients with physical status I and II according to American Society of Anesthesiologists (ASA). They were scheduled for elective cesarean section under general anesthesia to last at least 60 minutes.

Patients with gastrointestinal disease, drug allergy, addiction, complicated pregnancy, and those who had used to take antiemetic drug within one month before the cesarean section were excluded from the study. The sample size was calculated, based on a power of 0.95, a type one error of 0.05 and a d=0.8 (minimum difference of mean visual analogue scale for nausea between groups based on previous relevant clinical data), to be 32 cases in each group.

The patients were randomized using computer generated codes of random numbers with sampling of consecutive and eligible parturients. In cases of exclusion of a patient, the next case was assigned per schedule. Preoperative fluid therapy was based on 4.2.1 rule using 1/3-2/3 solution in all patients.[1]

Prior to the induction of anesthesia, continuous electrocardiogram (ECG), non-invasive arterial blood pressure, pulseoximetry and expiratory gas were monitored using a Hewlett-Packard monitor. Anesthesia was induced with sodium thiopental (5 mg/kg), succinyl choline (1.5 mg/kg) in all patients. Trachea was intubated with a cuffed tracheal tube. Anesthesia was maintained with a mixture of isoflorane (0.5 minimum alveolar concentration; MAC) and an O_2/N_2O ratio of 50/50. After the first twitch response in a train of four monitoring of ulnar nerve, atracurium (0.2 mg/kg) injected for neuromuscular blockade. The patients' were ventilated using a tidal volume 10 ml/kg, and respiratory rate was adjusted to give an end tidal carbon dioxide of 38-45 mmHg. After clamping the umbilical cord, the patients were randomly allocated into one of the three groups (F, E and C groups). Each group consisted of 32 parturients. In group F, Fentanyl was given as a bolus (2 µg/kg) and an infusion of 2 µg/kg/h. In group R, remifentanil was given as a bolus dose of 1 µg/kg followed by an infusion of 0.05 µg/kg/min. In group C, fentanyl (2 µg/kg) and morphine (0.1 mg/kg) were given as intravenous boluses.

All the drugs were labeled with the randomization number of the parturients. Administration of the drugs began right after clamp of the cord. After completion of the surgery, neuromuscular blockade was reversed with atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg). The participants were extubated in awaked state.

The patients and the staffs involved in the collection of data were unaware of the group assignment. In the cases of emergency, the anesthesiologist, who was responsible for the patient, had access to the nature of the drugs

administered to the patient.

On arrival in the recovery room, when the patient was amenable to evaluation, nausea was determined by an 10-point categorical scale, where 0 represented no nausea and 10 represented nausea as severe as it could be. The presence of nausea was reassessed at 4, 8, 12 and 24 hours after recovery. Nausea intensity was evaluated by VAS ranging from 0 (no pain) to 10 (worst pain imaginable).

Treatment of PONV consisted of metoclopramide (150 µg/kg intravenous), if there were more than two episodes of nausea or vomiting in less than 30 min. Pain score, systolic and diastolic blood pressures, frequency of vomiting, and opioid and metoclopramide consumptions were measured for each patient.

If analgesia was considered inadequate at any stage, the anesthesiologist could give additional blouse of 50 mg meperidine until VAS was less than 4.

Quantitative data were shown as mean±SD, qualitative data as counts and percentages. The quantitative data were analyzed using one-way Analysis of Variance (ANOVA). Where a significant difference was found with ANOVA, the source of the difference was located using Tukey test. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 11). A p value of <0.05 was considered statistically significant.

Results

Ninety-six patients completed the study. No patient was excluded from the study. There was no significant difference between groups receiving fentanyl, remifentanyl or fentanyl plus morphine in terms of age, weight, duration of gestation, parity, systolic and diastolic blood pressures, heart rate, or ASA physical status (table 1).

There was no significant difference between the three groups in terms of frequency of nausea, vomiting or mean nausea score at any time points (table 2). Also, none of patients was administered metoclopramide.

The three groups were not significantly

Table 1: The characteristics (mean±SD) of patients in groups (n=32 each) receiving fentanyl (group F), remifentanyl (group R) or fentanyl plus morphine (group C)

Variables	Group F	Group R	Group C	P value
Age (years)	27.9±5.7	26.1±4.6	26.7±5.3	0.55
Weight (kg)	72.4±10.8	73.1±12.2	71.5±9.3	0.31
Gestation (weeks)	37.4±2.2	37.5±2.1	37.3±3.3	0.83
SBP (mm Hg)	112.8±8.5	116.5±9	116.4±11.8	0.14
DBP (mm Hg)	66±8.1	67.1±7.3	65.3±6.3	0.18
HR(beat/min)	88.1±4.1	89.2±3.8	90.3±4.2	0.28
ASA I/II number	25/7	24/8	25/7	0.43
Parity	10	9	9	0.34

SBP: systolic blood pressure (mmHg), DBP: diastolic blood pressure (mmHg), HR: Heart rate (beat/min), ASA: American Society for Anesthesiologists

Table 2: The frequencies and percentages of nausea and vomiting, as well as visual analog scale (VAS) for nausea and pain at recovery, and 4 , 8 ,12 and 24 hours after caesarean section in groups (n = 32 each) receiving fentanyl (groups F), remifentanyl (group F) and fentanyl plus morphine (group C)

Time		Group F	Group R	Group C	P value
At recovery	Nausea (n, %)	6 (18.8%)	10 (31.3%)	11 (34.4%)	0.16
	Vomiting (n, %)	1 (3.1%)	2 (6.3%)	1 (3.1%)	0.38
	VAS (for nausea)	1.07±0.5	1.5±0.8	2.2±1.2	0.265
	VAS (for pain)	7.62±2.6	8.59±2.3	7.06±3.08	0.078
4 h after surgery	Nausea (n, %)	2 (6.3%)	1 (3.1%)	1 (3.1%)	0.38
	Vomiting (n, %)	0	0	0	
	VAS(for nausea)	0.88±0.02	0.53±0.01	0.35±0.01	0.832
	VAS(for pain)	6.71±2	7.15±2.2	6.15±2.4	0.206
8 h after surgery	Nausea (n, %)	0	0	2(6.3%)	0.06
	Vomiting (n, %)	0	0	0	
	VAS(for nausea)	0	0	0.49	0.132
	VAS(for pain)	5.78±2.21	5.43±2.28	5.68±2.44	0.828
12 h after surgery	Nausea (n, %)	0	0	1 (3.1%)	0.18
	Vomiting (n, %)	0	0	0	
	VAS (for nausea)	0	0	0.17	0.372
	VAS (for pain)	4.53±2.39	4.5±2.52	4.12±2.04	0.741
24 h after surgery	Nausea (n, %)	0	0	1 (3.1%)	0.18
	Vomiting (n, %)	0	0	0	
	VAS (for nausea)	0	0	0.17	0.382
	VAS (for pain)	2.87±1.64	2.75±1.66	2.56±1.84	0.766
Meperidine used (mg)		101.2±2 9.5*	138.1±43.7	121.8±35.9*	0.001

VAS: visual analogue scale. *denotes significant difference from remifentanil-treated group

different in terms of pain scores (VAS) measured at all time points. However, the VAS for pain in group R was insignificantly more than group F and C at recovery and 4 hours after surgery. Also, mepridine consumption in remifentanyl group was significantly more than that in fentanyl or fentanyl plus morphine groups at 24 hours after surgery (P=0.001) (table 2). There was no difference among the three groups in terms of hemodynamic parameters such as blood pressure or heart rate in all measurements after the surgery.

Discussion

The findings of the study show that mean VAS for nausea and frequency of nausea and vomiting did not differ significantly between three groups. Previous studies investigating the incidence of PONV after general anesthesia with remifentanil have yielded conflicting results.[12,13] These findings are similar to that of a previous study, which showed that there was no significant difference between the number of postoperative vomiting episodes in groups receiving fentanyl or remifentanyl.[3] However, our findings are different from another study, which showed that compared with propofol and remifentanyl, propofol and fentanyl anesthesia resulted in a higher incidence of PONV and requirements of antiemetic drugs in 2 to 12 hours after plastic surgery.[2]

In most women, mild to moderate nausea and vomiting are especially common until approximately 16 weeks inside pregnancy. Hyperemesis gravidarum is defined as severe vomiting during pregnancy. It can produce weight loss, dehydration, alkalosis, and hypokalemia. Hyperemesis gravidarum appears to be related to high or rapidly rising serum levels of pregnancy-related hormones. Although the exact stimulus is unknown, putative culprits include human chorionic gonadotropin, estrogens, progesterone, leptin, placental growth hormone, prolactin, thyroxine and adrenocortical hormones.[10] Hyperemesis gravidarum affects 0.5% to 1% of pregnancies, and seropositivity for Helicobacter pylori is more common in women with this pathology.[14]

Another study,[15] showed that the incidence of POV in patients receiving remifentanil did not increase. The authors attributed such an effect by remifentanil to the short duration of the study.[15]

Dershwitz et al showed that PONV were often multifactorial in origin. Some variables such as the type of surgery and drugs used have an important influence on the incidence of PONV.[4] For example, when an infusion of remifentanil was used during the administration of a regional anesthetesia for orthopedic or urogenital surgery, the incidence of PONV was 60% and 21%, respectively.[16] The administration of other opioids, intravenous or volatile anesthetics like propofol, barbiturate and so on, might have influence on PONV.[17-20] A recent study compared PONV after equipotent doses of alfentanil, fentanyl and sufentanil in large number of out-patients, in which thiopental sodium was used for induction, and nitrous oxide with isoflurane were used for maintenance of anesthesia.[21] The study showed that the incidence of PONV ranged from 12% to 35%.

The study shows that patients who experienced PONV might have received higher doses of opioids. In an earlier study on volunteers, a high incidence of nausea was observed.[11] and persisted for hours in some of the subjects. However, some of the subjects in that study,[11] received much higher doses of remifentanil than that used in the present study. Also, In our study, there was no significant difference between the three groups in terms of pain score at all the times. The mean VAS for pain and meperidine consumption in group R was insignificantly more than that in group F at recovery and 4 hour after surgery.

Similar to our findings, an earlier study found that compared to remifentanil, fentayl used for balanced anesthesia could produce a better early postoperative analgesia.[3] The differential effects of remifentanil may be due to its short half-life, which influences the time course of pain relief compared to longer acting opioids.[1]

The findings of the present study should be considered in light of two limitations. One limitation is that the effect of opioids on clinical outcome variables such as time to discharge or number of unexpected hospital readmissions could not be addressed, because all patients remained in the hospital for 24 hours after discharge from the recovery area. The second limitation is the lack of both strict follows up methodology and proper statistical power and small sample size. Therefore, further studies with different methodologies and appropriate sample size might be required to evaluate PONV and pain.

Conclusion

The findings of the present study may suggest that compared with fentanyl, remifentanil had no effect on PONV and postoperative pain relief. They also show that early postoperative analgesia was better with fentanyl, and postoperative meperidine consumption was signifi-

cantly less with fentanyl than with remifentanil or combined fentayl and morphine.

Conflict of Interest: None declared

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