Retrospective Study

Comparing the Effects of Fentanyl, Sufentanil, and Butorphanol Combined With Flurbiprofen Axetil on Postoperative Intravenous Patient-controlled Analgesia Post Cesarean Delivery

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Background: The analgesic effects between fentanyl, sufentanil, and butorphanol combined with flurbiprofen axetil on postoperative patient-controlled intravenous analgesia (PCIA) after cesarean delivery has never been evaluated.

Objectives: To evaluate the postoperative analgesic efficacy of selected PCIA formulae.

Study Design: This is a retrospective study.

Setting: Department of Anesthesiology, Shenzhen Second People's Hospital, a medical center in Shenzhen City, Guangdong Province, People's Republic of China.

Methods: From January 2022 through October 2023, the records of 463 patients who underwent a cesarean delivery were reviewed at Shenzhen Second People's hospital. All used a postoperative PCIA formula combined with flurbiprofen axetil and an antiemetic (ondansetron or tropisetron). The patients were placed into one of 3 groups: the Fentanyl Group (fentanyl plus flurbiprofen axetil plus ondansetron or tropisetron, 178 patients); the Sufentanil Group (sufentanil plus flurbiprofen axetil plus ondansetron or tropisetron, 159 patients); or the Butorphanol Group (butorphanol plus flurbiprofen axetil plus ondansetron or tropisetron, 126 patients). The primary data collected were the perioperative use of analgesics, postoperative Visual Analog Scale score, and no differences in adverse reactions were observed, except for the incidence of nausea and vomiting.

Results: A significant difference was found between using epidural analgesics (such as morphine) and intravenous analgesics (such as butorphanol, flurbiprofen axetil, tramadol, parecoxib, and dexmedetomidine). There was no difference among the groups in postoperative Visual Analog Scale scores at 24 hours and 48 hours post cesarean delivery. There also was no difference in adverse reactions.

Limitations: Our study was limited by a small sample size and did not differentiate the Visual Analog Scale scores between states of rest and movement.

Conclusion: The analgesic effect in patients who underwent cesarean delivery is similar when using different postoperative PCIA formulae. Although butorphanol displayed no analgesic advantage over fentanyl and sufentanil postoperatively, it caused fewer postoperative nausea and vomiting incidences than fentanyl and sufentanil.

Key words: Fentanyl, sufentanil, butorphanol, flurbiprofen axetil, postoperative patient-controlled intravenous analgesia, cesarean delivery, analgesic drugs, postoperative pain management

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Associated with tissue damage or potential tissue damage, pain is the body's defensive response to harmful stimuli. The cause of postoperative pain is considered to result from tissue damage and accompanying inflammation. Cesarean delivery (CD) is an effective measure to solve labor dystocia.

According to a survey conducted by the World Health Organization, the People's Republic of China has the highest CD rate in the world, up to 46.2%, which is much higher than the average CD rate of 27.3% worldwide (1). The pain of CD primarily consists of 2 main components: physical pain and visceral pain; the surgical incisions and uterine contractions cause the most pain within 24 hours postsurgery (2). The presence of surgical trauma or postoperative pain can induce stress responses in the body. These stress responses complicate postoperative recovery and have a negative effect on prognosis. Good postoperative analgesia can relieve inflammatory stress responses and facilitate recovery. The use of postoperative patient-controlled intravenous analgesia (PCIA) can relieve incision pain and visceral pain, enhance postoperative recovery, and improve maternal satisfaction and comfort.

Fentanyl is a powerful analgesic with a potency of 75–125 times that of morphine. Fentanyl stimulates opioid receptors, produces analgesic effects, and is widely used in perioperative pain management (3). A large number of opioid receptors (including μ, δ, and κ receptors) are present in the central nervous system and in the peripheral gastrointestinal tract, fentanyl can also cause adverse reactions such as nausea, vomiting, itching, drowsiness, and circulatory and respiratory depression when it binds with these receptors (4).

As a derivative of fentanyl, sufentanil has more affinity for opioid receptors, especially with a higher affinity for binding to the μ receptor; its affinity is about 10 times that of fentanyl (5). With a clinical analgesic effect 5 times greater than fentanyl, sufentanil is considered the strongest opioid analgesic that can act on the human body (6).

Butorphanol is a potent opioid analgesic that can fully activate κ receptors and partially activate μ receptors, thereby producing analgesia (7). The finding of one study showed butorphanol is commonly used for analgesia post CD and is effective at reducing postoperative pain (8). There is a long-lasting effect of butorphanol, especially for inhibiting the pain caused by uterine contractions (9).

As a nonsteroidal anti-inflammatory drug, flurbiprofen axetil acts as an analgesic and is carried by lipid microspheres. It can selectively aggregate at the inflammatory site or surgical incision after intravenous injection, and offer strong efficacy, fast onset, and long duration, as well as the potential to alter the distribution of drugs within the body, thus achieving targeted treatment effects (10). The combined use of flurbiprofen with an opioid can enhance analgesic effect and can be safely used for CD, which might reduce opioid dosages and their side effects in clinical practice (11).

Patients undergoing CD can benefit from intravenous fentanyl, sufentanil, or butorphanol for PCIA. Currently, most PCIA formulae consist of fentanyl, sufentanil, and butorphanol with flurbiprofen axetil for postoperative analgesia post CD in our department. Since there is no literature comparing their analgesic effects in CD, we undertook this study in order to compare the analgesic effects of 3 PCIA formulae, aiming to provide a new insight into clinical pain management.

Methods

Grouping and Patients

A total of 463 maternal patients who underwent CD from January 2022 through October 2023 were reviewed at Shenzhen Second People's hospital. All of them received CD and PCIA. The Included patients were those with access to PCIA post CD during the time periods as described above. Exclusion criteria were: 1) patients with severe organ dysfunction and difficulty in observing pain symptoms; 2) stroke, cerebral infarction, or craniocerebral surgery histories; 3) patient-controlled epidural analgesia following CD; 4) other PCIA formulae except for fentanyl, sufentanil, or butorphanol combined with flurbiprofen axetil; 5) ectopic pregnancy; 6) patients who received general anesthesia and/or a peripheral nerve block; and 7) those transferred to the intensive care unit post CD.

According to the different PCIA formulae, they were divided into 3 groups: Fentanyl Group (fentanyl plus flurbiprofen axetil plus ondansetron or tropisetron, 178 patients); Sufentanil Group (sufentanil plus flurbiprofen axetil plus ondansetron or tropisetron, 159 cases); Butorphanol Group (butorphanol plus flurbiprofen axetil plus ondansetron or tropisetron, 126 cases).

Ethics

Our study was reviewed and approved by the Ethics Committee of Shenzhen Second People's Hospital (Approval No. 2024-138-01JP). It was conducted in ac-

cordance with the ethical standards of the ethics committee of Shenzhen Second People's Hospital and applicable Republic of China laws and regulations, as well as the ethical standards of the Declaration of Helsinki and international ethical guidelines for biomedical research involving human participants.

Analgesia Strategies

All patients received spinal anesthesia. Post-CD, the patients who returned to the ward were treated with one of 3 PCIA formulae as follows: Formula One—fentanyl 400 μg–1000 μg plus flurbiprofen axetil 150 mg–350 mg plus ondansetron 8 mg–16 mg or tropisetron 10 mg–15 mg plus appropriate normal saline; Formula 2—sufentanil 50 μg–100 μg plus flurbiprofen axetil 100 mg–350 mg plus ondansetron 4 mg–16 mg or tropisetron 5 mg–15 mg plus appropriate normal saline; Formula 3 — butorphanol 6 mg–12 mg plus flurbiprofen axetil 150 mg–250 mg plus ondansetron 8 mg–16 mg or tropisetron 10 mg plus appropriate normal saline for a total solution of 100 mL. The PCIA pump connected to the patient delivered a background dose of 2 mL/h and an additional dose of automatic analgesia 1.5 mL–2 mL/15 min–20 min.

Data Collection

Patient data collected included 1) gender, age, height, weight, body mass index (BMI [kg/m^2]); 2) the patient's history before and during pregnancy and at present; 3) the name of the surgical procedure, time of operation, length of incision, number of CD occurrences; 4) PCIA formula, Visual Analog Scale (VAS) score at 24 hours and 48 hours post CD; 5) any additional use of analgesics post-CD; 6) and post-CD complications, including dizziness, nausea and vomiting, limb numbness, urinary retention, pruritis, and extrapyramidal side effects.

Statistical Analysis

All data are expressed as quantitative or qualitative. One-way Analysis of Variance (ANOVA) and χ^2 tests were performed to analyze the data. $P > 0.05$ was considered to be statistically different. IBM SPSS Statistics 19.0 (IBM Corp.) was used for the statistical calculations.

Results

Patient Characteristics

There were no significant differences in age (Figs. 1A, 1B), height (Fig. 1C), weight (Fig. 1D), and BMI (Fig. 1E) among the groups (Table 1). In the absence of other serious complications (heart disease, stroke, cerebral infarction, etc.); patients with hypertension or diabetes during pregnancy were more likely to be found. Overall, there were no differences in the incidence of hypertension; the occurrence of diabetes mellitus differed significantly among the subgroups (Table 1 and Fig. 1F).

Cesarean Delivery Duration and Analgesic Use

No difference was noted in the CD duration (Fig. 2A), incision length (Fig. 2B), and the number of CD occurrences (Fig. 2C) among all 3 groups (Table 2). There were significant differences in the use of epidural analgesics (e.g., morphine) and intravenous analgesics (e.g., butorphanol, flurbiprofen, tramadol, parecoxib [not US FDA approved], dexmedetomidine); the administration of combined intravenous analgesics also differed significantly among the groups (Table 2 and Figs. 2D–2F).

Post Cesarean Delivery VAS Score and Adverse Reactions

The VAS score in each group showed no difference in the resting state of patients at 24 hours and 48 hours post-CD (Table 3 and Figs. 3A and 3B). Apart from the occurence of nausea and vomiting, no group had a significant level of post-CD adverse reactions (Table 3 and Figs. 3C and 3D).

Discussion

In our study, 463 patients underwent one of 3 different PCIA post-CD surgery. There was a significant difference in the use of epidural analgesics (such as morphine) and intravenous analgesics (such as butorphanol, flurbiprofen axetil, tramadol, parecoxib, and dexmedetomidine) among the 3 groups. The post-CD VAS scores at 24 hours and 48 hours, as well as the adverse reactions were similar (except for nausea and vomitting) between the 3 groups.

There was significant difference in gestational diabetes mellitus among the 3 groups (Table 1 and Fig. 1). It has been reported that 19.1% of women of child bearing age in the People's Republic of China have gestational diabetes mellitus (12), which matches the rate of 19.2% (89/463) in our study. Such a high incidence of gestational diabetes mellitus is attributed to insulin resistance, metabolic changes, and genetic inheritance (13). This suggests that providers should pay more attention to the perioperative care of patients with gestational diabetes mellitus.

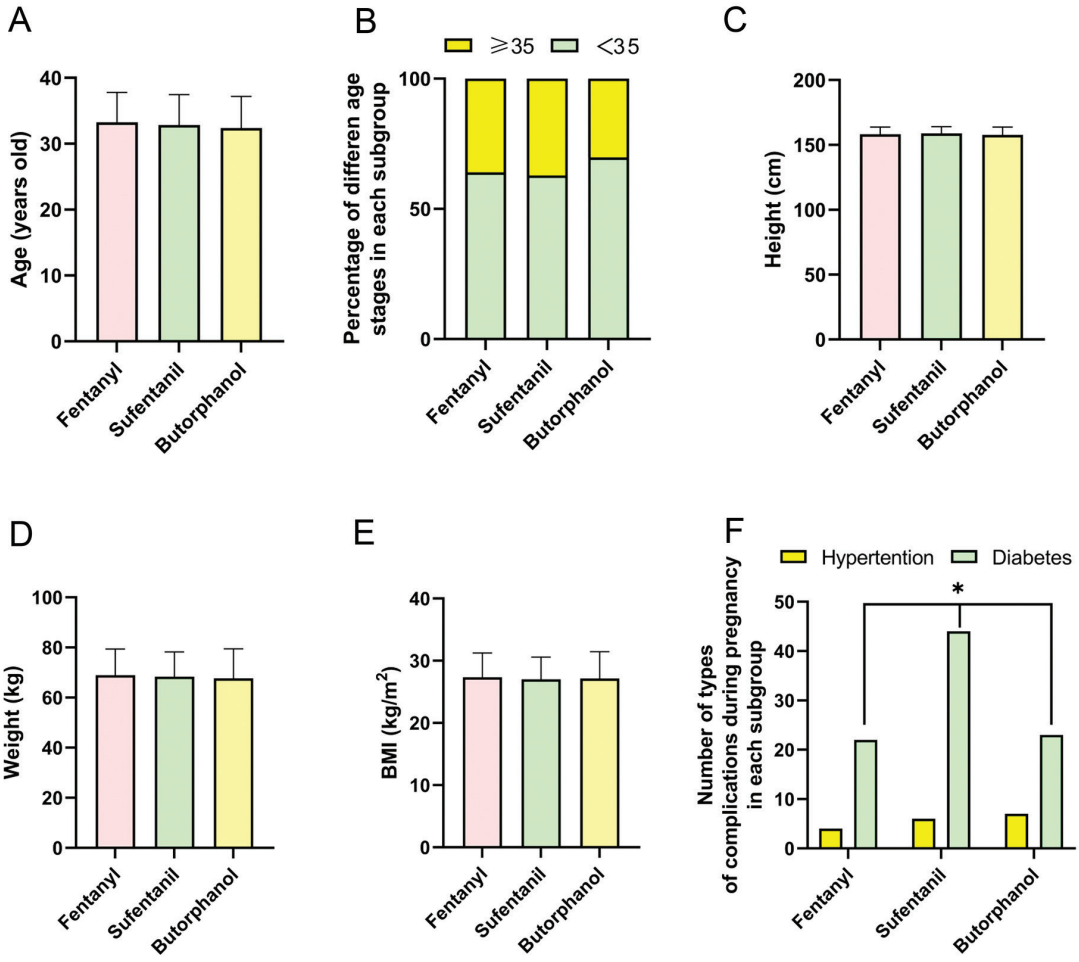

Fig. 1. *Patient characteristics. (A) Age (B) Percentage of different age stages in each subgroup (C) Height (D) Weight (E) Body mass index (BMI [kg/m2]) (F) Number of types of complications during pregnancy in each subgroup. *There were significant differences among the groups (P < 0.05).*

Table 1. *Characteristics of Patients*

Group		Fentanyl group	Sufentanil group	Butorphanol group	*P* value
Gender (%)	Female	178 (100%)	159 (100%)	126 (100%)	
Age (years)	Mean ± SD < 35 ≥ 35	33.24 ± 4.54 64% (114/178) 36% (64/178)	32.86 ± 4.59 62.9% (100/159) 37.1% (59/159)	32.38 ± 4.80 69.8% (88/126) 30.2% (38/126)	0.231
Height (cm)	Mean±SD	158.31 ± 5.45	158.85 ± 5.18	157.79 ± 5.93	0.298
Weight (kg)	Mean±SD	68.95 ± 10.44	68.34 ± 9.87	67.71 ± 11.78	0.66
BMI (kg/m^2)	Mean±SD	27.49 ± 3.91	27.07 ± 3.57	27.16 ± 4.29	0.577
Hypertension (before pregnancy)		0	0	0	
Diabetes (before pregnancy)		0	0	0	
Hypertension (during pregnancy)		2.2 % (4/178)	3.8% (6/159)	5.6% (7/126)	0.318
Diabetes (during pregnancy)		12.4% (22/178)	27.7% (44/159)	18.3% (23/126)	0.002*

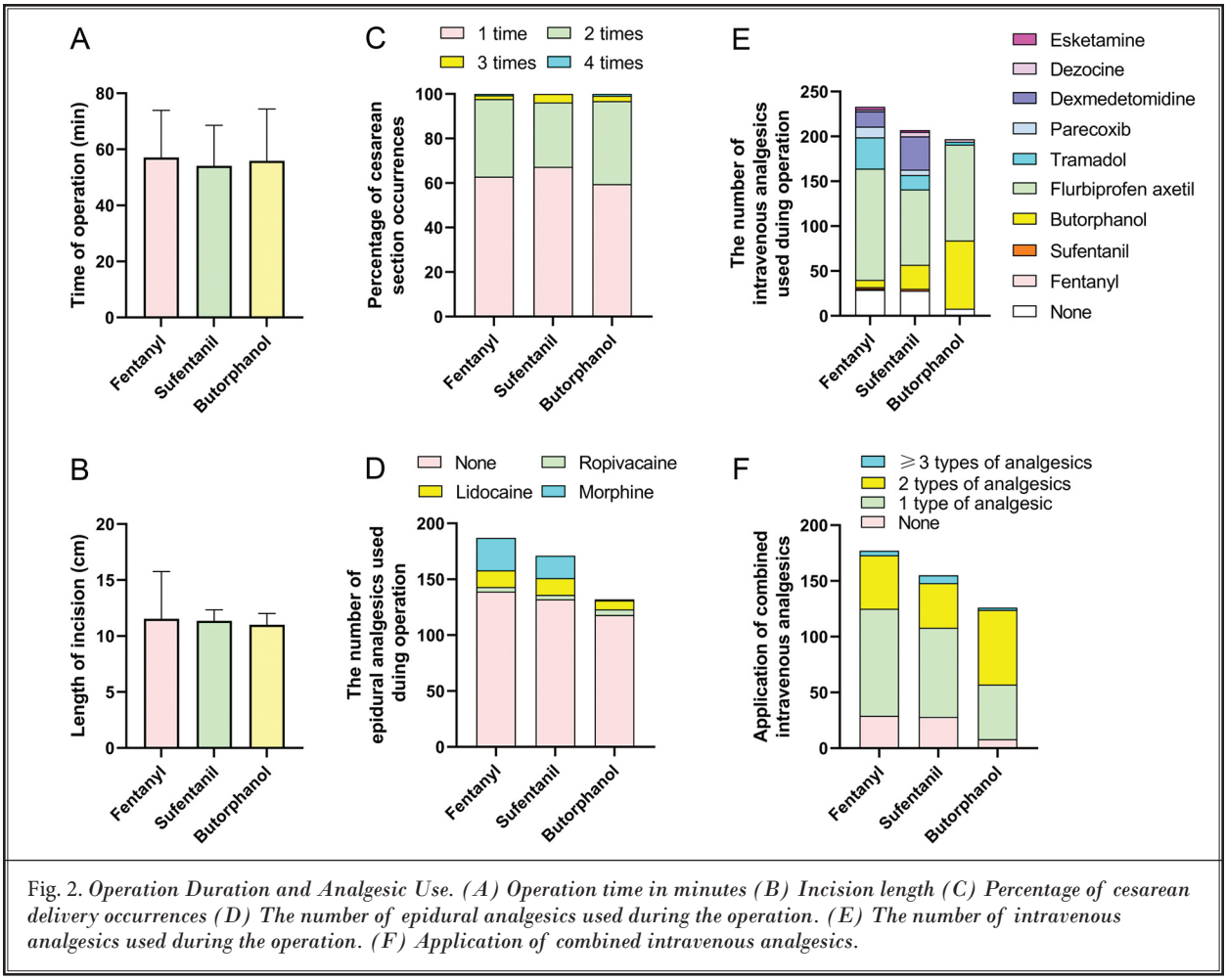

Fig. 2. *Operation Duration and Analgesic Use. (A) Operation time in minutes (B) Incision length (C) Percentage of cesarean delivery occurrences (D) The number of epidural analgesics used during the operation. (E) The number of intravenous analgesics used during the operation. (F) Application of combined intravenous analgesics.*

Multiple analgesic drugs with different mechanisms of action may be used in combination, thereby exerting an additive or synergistic analgesic effect. With flurbiprofen axetil in PCIA, we provided multimodal analgesia with our analgesic formula.

As a lipid emulsion, flurbiprofen axetil contains lipid microspheres, which can aggregate in inflammatory sites, surgical incisions, and vascular emboli following intravenous injection. It features high effectiveness, rapid action, and a prolonged effect. It can alter drug distribution within the body, enabling targeted treatment (10).

The analgesic effect was similar across all three groups in our study (Table 3 and Fig. 3). The possible explanation is that the current perioperative analgesia mainly utilizes multi-mode analgesia, incorporating epidural and intravenous techniques (Table 2 and Fig. 2).

Moreover, all 3 groups did not show any differences in adverse reactions (such as dizziness, constipation, urinary retention, limb numbness, pruritis, respiration depression, extrapyramidal syndrome) except for nausea and vomiting. Opioids such as fentanyl are rarely transferred to breast milk (14), which benefits breastfeeding after CD, however, de Boer, et al (15) reported that opioid-caused nausea and vomiting are occur 50% and 20% of the time, respectively. Fentanyl induces nausea and vomiting by stimulating the medullary center and increasing the sensitivity of the vomiting center though the vestibular nervous system. Opioid receptor agonists can also be responsible for nausea, causing it by affecting gastric and duodenal motility (16). In our study we found that there was a higher incidence of post-CD nausea and vomiting in the butorphanol group (1.6%) than with fentanyl (7.9%) or sufentanil (7.5%). We incorporated antiemetic drugs into our analgesic formula, which can greatly suppress nausea and vomiting. Our findings align with previous research indicating that fentanyl has a similar incidence of nausea and vomiting compared to sufentanil (6), while butorphanol has a lower incidence than sufentanil (17,18).

Table 2. *Duration of operation and use of analgesics*

Group		Fentanyl group	Sufentanil group	Butorphanol group	*P* value
Time of operation (min)	Mean ± SD	57.10 ± 16.82	54.09 ± 14.45	55.92 ± 18.43	0.158
Length of incision (cm)	Mean ± SD	11.55 ± 4.23	11.35 ± 0.98	11 ± 1.01	0.221
Number of cesarean section occurrences	1 time 2 times 3 times 4 times	62.9% (112/178) 34.8% (62/178) 1.7% (3/178) 0.6% (1/178)	67.3% (107/159) 28.9% (46/159) 3.8% (6/159) 0	59.5% (75/126) 37.3% (47/126) 2.4% (3/126) 0.8% (1/126)	0.558
Epidural analgesic	None	78.1% (139/178)	83.0% (132/159)	93.7% (118/126)	0.0012*
	Ropivacaine	2.2% (4/178)	2.5% (4/159)	4.0% (5/126)	0.654
	Lidocaine	8.4% (15/178)	9.4% (15/159)	6.3% (8/126)	0.636
	Morphine	16.3% (29/178)	12.6% (20/159)	0.8% (1/126)	0.0001*
Intravenous analgesic	None	16.3% (29/178)	17.6% (28/159)	6.3% (8/126)	0.0135*
	Fentanyl	0.6% (1/178)	0	0	0.448
	Sufentanil	1.1% (2/178)	1.3% (2/159)	0	0.466
	Butorphanol	4.5% (8/178)	17% (27/159)	60.3% (76/126)	0.0001*
	Flurbiprofen axetil	69.7% (124/178)	52.8% (84/159)	84.9% (107/126)	0.0001*
	Tramadol	19.7% (35/178)	10.1% (16/159)	2.4% (3/126)	0.0001*
	Parecoxib	6.7% (12/178)	3.8% (6/159)	0	0.0112*
	Dexmedetomidine	9.6% (17/178)	23.3% (37/159)	0	0.0001*
	Dezocine	1.1% (2/178)	3.1% (5/159)	2.4% (3/126)	0.4353
	Esketamine	1.7% (3/178)	1.3% (2/159)	0	0.3618
Application of combined intravenous analgesics	1 type of analgesic	53.9% (96/178)	50.3% (80/159)	38.9% (49/126)	0.0001*
	2 types of analgesics	27.0% (48/178)	25.2% (40/159)	53.2% (67/126)	
	≥ 3 types of analgesics	2.2% (4/178)	4.4% (7/159)	1.6% (2/126)	

Table 3. *Postoperative VAS score and adverse reactions*

Group		Fentanyl group	Sufentanil group	Butorphanol group	*P* value
VAS score (24h after surgery)	Mean ± SD	2.08 ± 0.40	2.14 ± 0.69	2.06 ± 0.44	0.303
VAS score (48h after surgery)	Mean ± SD	2.04 ± 0.26	1.99 ± 0.08	2.05 ± 0.31	0.362
Use of additional analgesics in the postoperative ward (%)	None	96.6% (172/178)	95.0% (151/159)	97.6% (123/126)	0.174
	Sometimes (≤ twice)	0	2.5% (4/159)	1.6% (2/126)	
	Frequently (> twice)	3.4% (6/178)	2.5% (4/159)	0.8% (1/126)	
Postoperative adverse reactions	None	92.1% (164/178)	91.8% (146/159)	97.6% (123/126)	0.0902
	Nausea and vomiting	7.9% (14/178)	7.5% (12/159)	1.6% (2/126)	0.0479*
	Dizzy	0	0	0.8% (1/126)	0.262
	Constipation	0	0	0	
	Urinary retention	0	0	0	
	Limb numbness	0	0	0	
	Skin itch	0	0.6% (1/159)	0	0.384
	Respiration depression	0	0	0	
	Extrapyramidal syndrome	0	0	0	

Butorphanol acts as an opioid agonist-antagonist and is mainly analgesic due to the antagonizing action of κ receptors. It has antagonistic or partial agonist effects on μ receptors, and has no obvious action on δ receptors (7). Furthermore, butorphanol is also superior to pure opioid receptor agonists when it comes to inhibiting visceral pain (17); it also has a lower incidence of side effects such as nausea and vomiting (17,19), which may be because butorphanol primarily activates κ receptors and reduces the effect of μ receptors on gastrointestinal transit (20).

Limitations

This study has some deficiencies. First, the sample size was small and so may be inadequate. Second, we didn't distinguish the VAS score during resting and movement states. Third, the post-CD follow-up staff was not fixed, so evaluation methods may have varied slightly, which may have caused a bias in the results.

Conclusion

In summary, butorphanol did not have any advantage in analgesia over fentanyl and sufentanil post-CD, but it did have lower nausea and vomiting rates.

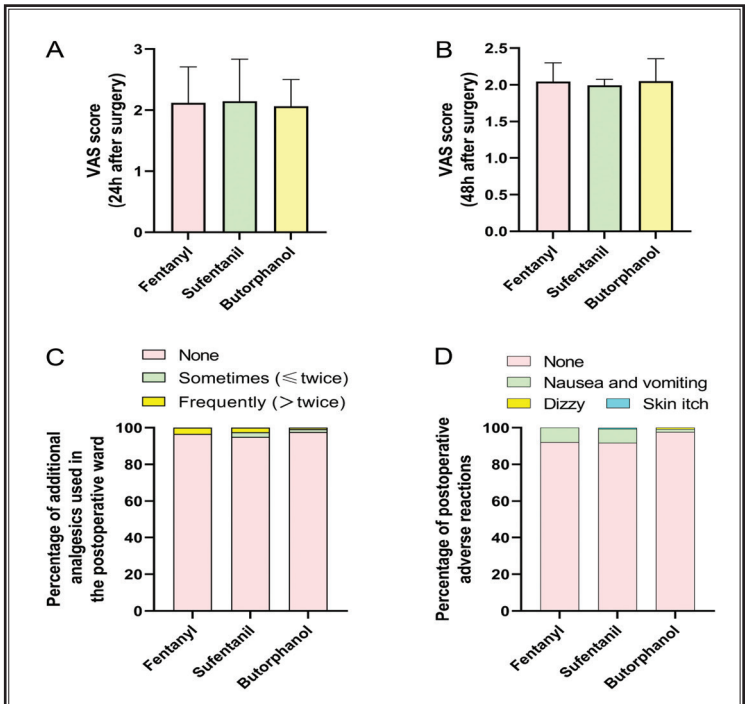

Fig. 3. *Postoperative Visual Analog Scale VAS score and adverse reactions. (A) VAS scores at 24 hours postsurgery (B) VAS scores at 48 hours postsurgery (C) Percentage of additional analgesics used in the postoperative ward (D) Percentage of postoperative adverse reactions .*

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Author Contributions

Changjian Liao conducted the protocol, analyzed the data, and drafted the manuscript. Guangyan Li, Xiaojing Chen, Yingmei Liu, Zhongbo Lu, Jinglei Gao, and Xiaofeng Huang collected the data. Xinping Yang analyzed the data. Zhiheng Liu edited the manuscript. Xiongjuan Li designed the protocol, analyzed the data, and revised and supervised the writing of the manuscript.

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