Asian Journal of Medicine and Health

Volume 21, Issue 10, Page 146-159, 2023; Article no.AJMAH.103079
ISSN: 2456-8414

Parecoxib, Dezocine and Epidural Morphine for Perioperative Multimodal Analgesia in Cesarean Section: A Randomized Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2023/v21i10888

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/103079

Original Research Article

Received: 01/06/2023
Accepted: 05/08/2023
Published: 14/08/2023

ABSTRACT

Objective: To observe the effect of multimodal analgesia with single venous injection of parecoxib sodium and single epidural injection of morphine combine with dezocine intravenous infusion on the maternal pain, the adverse effects, the maternal activity and lactation and the stress response after cesarean section.

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Methods: The 90 cases of pregnant were randomly divided into three groups: Morphine and Dezocine (MD) group, Parecoxib sodium and Dezocine (PD) group, Parecoxib sodium, Morphine, and Dezocine (PMD) group. There were 30 cases in each group. The following three analgesic methods and their combinations were used: single epidural injection of morphine 1.5 mg, single intravenous injection of parecoxib 40 mg and intravenous analgesia with dezocine 0.5 mg/kg. Postoperative pain, adverse effects, maternal activity and breastfeeding, and serum substance P levels were observed.

Results: These were statistically significant in the differences of VAS of incision pain at 8 h and 12 h after surgery ($P < 0.05$), in which the VAS in PMD group were lower than that in PD group and MD group, and in which the VAS in PD group was higher than that in MD group. These were statistically significant in the differences of VAS of uterine contractile pain at 8h and 12 h after surgery ($P < 0.05$), in which the VAS in PMD group were lower than that in PD group and MD group, and in which the VAS in PD group was lower than that in MD group. The time of starting to get out of bed after surgery was earlier in the PMD group than in the PD and MD groups ($P < 0.05$). The number of steps taken by mothers within 2 days after surgery was higher in the PMD group than in the PD and MD groups ($P < 0.05$). The step count within two days post-surgery was higher in the PMD group than in the PD and MD groups ($P < 0.05$). The serum substance P levels at the end of surgery and 1 day after surgery were lower in the PMD and PD groups than in the MD group ($P < 0.05$). The differences in the number of breastfeeding times within two days after surgery were statistically significant among the three groups ($P < 0.05$), with that in the PMD group（16.27±2.71）having been higher than in the PD group（12.63±1.67）and MD group（11.03±1.81）, and that in the MD group being higher than in the PD group.

Conclusion: The single intravenous sodium parecoxib combined with single epidural morphine and dezocine intravenous analgesia can better reduce the incision pain and uterine contractile pain after cesarean section, promote maternal postoperative off-bed activity and breast-feeding times to newborn.

Keywords: Parecoxib sodium; morphine; dezocine; multimodal analgesia; cesarean section; substance P.

1. INTRODUCTION

Postoperative analgesia after a cesarean section requires effective painkilling and facilitates early maternal postoperative ambulation and breastfeeding. In addition, postpartum complications, such as venous embolism, must be prevented [1,2]. After a cesarean section, the traditional epidural injection of opioids, combined with low concentrations of local anesthetics, may lead to muscle weakness or numbness in the lower extremities, affecting early ambulation and having a detrimental impact on early recovery and caring for the newborn [2,3]. An epidural injection of morphine is an effective option with an excellent safety profile. When this approach is adopted, adding a local anesthetic does not appear to benefit but may increase the incidence of adverse reactions [3]. Epidural analgesia with opioids controls post-cesarean pain, improving maternal mobility and interaction with the newborn [4]. Therefore, a single-bolus epidural injection of morphine with small doses of intravenous analgesia may be administered and promoted.

Dezocine is a partial μ-receptor and κ-receptor agonist with analgesic effects comparable to or slightly more potent than morphine but with fewer side effects [5] and has been used for postoperative analgesia following cesarean delivery [6]. A previous study by the authors found that a single-bolus epidural injection of morphine combined with intravenous dezocine could achieve a better analgesic effect. This not only reduced the dosage of dezocine but also significantly reduced the incidence of lower limb numbness and immobility, urinary retention (compared with epidural patient-controlled analgesia [PCA]), and increased the number of maternal breastfeeding sessions for the newborn [7,8]. The research also found that a single-bolus epidural injection of morphine combined with intravenous dezocine analgesia reduced the incidence of postpartum depression, [9] an approach recently applied in China [10]. However, the authors found in their clinical work during the past decade that while the present treatment had a satisfactory analgesic effect on somatic pain, it was associated with a high incidence of uterine contraction pain.

Therefore, the present study combined three modes of postoperative analgesia—i.e., an intravenous injection of parecoxib sodium, a single-bolus epidural injection of morphine, and intravenous dezocine PCA—to observe their effects on postoperative pain, adverse reactions, maternal mobility, and breastfeeding. Stress responses were also reviewed to provide a basis for the clinical selection of analgesia in cases of cesarean delivery.

2. MATERIALS AND STUDY METHODS

2.1 Case Selection

2.1.1 Study participants

A total of 90 women with an American Society of Anesthesiologists (ASA) grade I–II physical classification who underwent an elective cesarean section under combined spinal-epidural anesthesia (CSEA) were enrolled in the study. The participants' ages ranged from 20 to 39 years, and their body weights were from 50 to 80 kg. The gestational age ranged from 37 to 41 weeks and comprised full-term singleton births. The participants had no contraindications to endotracheal anesthesia; no history of relevant drug allergies or of drug or alcohol abuse; no peptic ulcer or gastrointestinal hemorrhage; no serious liver, kidney, or cardiopulmonary impairments; no inflammatory bowel disease; and no history of having received analgesic or sedative medication after pregnancy. All participants participated voluntarily in the study, and patients completed the written informed consent form for inclusion in the research. The study was approved by the ethics committee of the Foshan Second People's Hospital, Guangdong Province, China.The number of ethics document is KL2020030.

2.1.2 The exclusion criteria were as follows

Patients with high-risk pregnancies, e.g., a history of a previous cesarean section, breast development defects, pregnancy-induced hypertension, and severe fetal distress, were excluded from the study. Women who could not cooperate during the research observations, those who underwent surgery for longer than 120 min, and those who experienced a poor analgesic response due to prolapsed analgesia catheters or venous extravasations were excluded from the present study.

2.1.3 The grouping method was as follows

The random number method was adopted; set group numbers were sealed in envelopes and opened before conducting the experiment.

According to the results that the incision VAS scores of three groups of pre-study are : 1.55 ± 0.90,1.71 ± 1.05,1.51 ± 0.98,respectively. We set thatα=0.05, power=1- β =0.9,The MEDSCI simple calculation program to used to get the sample size for each group being 26, considering the loss-to-visit rate of 20%, we set 30 cases for each group.The 90 enrolled maternal cases were randomly allocated to three groups of 30 each, i.e., the morphine and dezocine (MD) group, the parecoxib sodium and dezocine (PD) group, and the parecoxib sodium, morphine, and dezocine (PMD) group acording to random number method, the group number was put into the envelope, before the implementation of the study, a nurse who did not participate in the later study opened the envelope and enrolled the puerpera in the three groups and the later data collection of this studysuch as ininal pain and unterun contract pain judge by VAS was performed by the doctor who did not know the grouping of the puerpera.

2.1.4 Interventions

Patients in the MD group were treated with a single epidural injection of 1.5 mg of morphine and intravenous PCA of 0.5 mg/kg dezocine after surgery. Patients in the PD group were given a single intravenous injection of 40 mg of parecoxib sodium and intravenous PCA of 0.5 mg/kg dezocine postoperatively. Patients in the PMD group were given a single intravenous injection of 40 mg of parecoxib sodium, a single-bolus epidural injection of 1.5 mg of morphine, and intravenous PCA of 0.5 mg/kg dezocine postoperatively.

2.2 Anesthesia was Delivered as Follows

No preoperative medication was administered in any of the three groups. After entering the operating room, the electrocardiogram, blood pressure (BP), and blood oxygen saturation (SpO2) values were routinely monitored using a Philips IntelliVue Mx800 (Philips Medizin Systeme Böblingen GmbH, Germany) in conjunction with the establishment of intravenous access.

Before administering anesthesia, 500 ml of Ringer's lactate solution was infused. All patients

were placed in the left lateral position, and the L 2-4 space was selected for performing CSEA using the needle-in-needle method. With the appearance of cerebrospinal fluid, 1.5–2 ml of 0.5% bupivacaine was slowly injected into the subarachnoid space (an isocratic solution with 2 ml of 0.75% bupivacaine + 1 ml of cerebrospinal fluid was prepared). With the epidural catheter dwelling in a cephalic direction, the patient was changed into a supine position with the left side elevated to 30° and the anesthesia plane not exceeding the T6 level. Intra-operative administration of phenylephrine, ephedrine, and atropine was determined according to BP and heart rate values.

Following the delivery of the fetus, the participants in all three groups were injected intravenously with 5 mg of diazepam, 2.5 mg of droperidol, and 5 mg of dezocine, while 1.5 mg of morphine (diluted to 5 ml with normal saline) was injected into the epidural cavity for patients in the MD and PMD groups, and 40 mg of parecoxib sodium (diluted to 5 ml with normal saline) was injected intravenously for patients in the PD and PMD groups. Selected patients in each group that did not receive a drug injection were injected with the same dose of normal saline, functioning as the study control.

Following surgery, different analgesic protocols were completed according to the participant grouping. All puerperae were guided for early contact with the newborn and initiation of breastfeeding after delivery, with mother and baby in the same room and breastfeeding occurring on demand.

2.3 Postoperative Analgesia

2.3.1 The postoperative analgesia protocol was as follows

Intravenous PCA of dezocine was provided for the three groups as a multimodal analgesic unit, with 0.5 mg/kg of dezocine added to normal saline to create a 100 ml injection for intravenous analgesia. The remaining two analgesic units were a single epidural injection of 1.5 mg of morphine and a single intravenous injection of 40 mg of parecoxib sodium.All maternal epidural catheters were withdrawn after injection of 1.5mg morphine into the epidural space. Oxytocin was administered for 20 μ after delivery of the fetus and was stopped at 1 hour postpartum.

2.3.2 The analgesic parameters were as follows

A electronic analgesia pump (100 ml volume) (YzMend, Nanjing Yangzi Medical Products Co., Ltd, China) was used in all three groups. The analgesic loading dose was 5 mg of intravenous dezocine with a background infusion of 2 ml/h and a PCA dose of 0. 5 m l/time, combined with a lockout time of 15 min and continuous administration for 48 h. After suturing the peritoneum, the analgesic pump was connected to the peripheral venous catheter to conduct intravenous PCA.

2.3.3 The following analgesics were used

Parecoxib sodium (Dynastat), 40 mg/vial (Pfizer Pharmaceuticals, Inc.; state medical permit no. J20080045); dezocine for injection, 5 mg/vial (Jiangsu Yangzijiang Pharmaceutical Co., Ltd.; state medical permit no. H20080329); morphine hydrochloride injection, 10 mg/vial (Hubei Yichang Renfu Pharmaceutical Co., Ltd.; state medical permit no. H20013351).

2.4 Observation Items and Indicators

2.4.1 The following maternal observations were performed

① The visual analog scale (VAS) score was used to assess incisional and uterine contraction pain at 2, 8, 12, 24, and 48 h, postoperatively. ② The number of cases with excessive vaginal bleeding (visually observable hemorrhage of >150 mL), nausea and vomiting, pruritus, dizziness and drowsiness, urinary retention (withdrawal of the urinary catheter > 6 h after surgery), and respiratory depression (defined as an SpO2 < 92% on 2–3 L/min of oxygen by nasal catheter) during the postoperative period were recorded. ③ The time to ambulation and the time to breastfeeding initiation after surgery, the step-counts (using step-counting software installed on the mother's cellphone), and the number of breastfeeding sessions within two days after surgery were recorded.

2.4.2 Sample collection and detection

One day before surgery, 2 ml of venous blood was collected. At the end of the surgery and one and two days after, blood was collected and naturally clotted for 10–20 min at room temperature and centrifuged for approximately

20 min (2,000–3,000 rpm). The supernatant was collected and stored in a low-temperature refrigerator below -30°C for further assay.

An enzyme-linked immunoassay method determined the serum concentration of substance P according to the instructions of the Human Substance P ELISA Kit (ZuoKey Biotechnology Co., Ltd., Zhongshan, Guangdong, China, Lot No.: AD20211108). The standards were set following a concentration gradient of 15 ng/L-240 ng/L. Three kinds of wells were set up: blank control wells without sample and enzyme standard reagents, standard wells, and wells for the samples to be tested. The standards were accurately spiked with 50 µl of sample on the wrapper plate of the enzyme marker (Labsystems Multiskan MS, Finland, instrument model 352). A sample diluent of 40 µl was added to the sample wells to be tested, followed by 10 µl of the sample to be tested, giving a final sample dilution of five times. The samples were added to the bottom of the ELISA plates without touching the wall of the wells and then mixed with gentle shaking. The well-mixed samples were sealed and incubated at 37°C for 30 minutes. A 30-fold concentrated washing solution was then diluted with distilled water and prepared for washing plates. After carefully removing the sealing membrane, the plates were washed five times with a washing solution and then blotted dry on filter paper. Subsequently, 50 µl of enzyme standard reagent was added to each well, except for the blank wells. The plates with the sealing membrane were incubated at 37°C for 30 minutes and washed five times as previously described. When the washing steps were finished, 50 µl of chromogenic agent A was added to each well, followed by 50 µl of chromogenic agent B. After gentle shaking and mixing, the reaction was developed for 15 minutes at 37°C, protected from light. Then, 50 µl of the termination solution was added to each well to terminate the reaction. Each well's absorbance (OD) value was measured sequentially at 450 nm with a blank as zero. The standard curve was plotted on the coordinate paper with the concentration of the standard as the horizontal coordinate and the OD value as the vertical coordinate. The corresponding concentration was found from the standard curve according to the OD value of the sample and then multiplied by the dilution factor, which is the actual concentration of the sample.

2.5 Statistical Methods

The SPSS Statistics version 23.0 software program (IBM, Armonk, NY, USA) was used for statistical processing. All the measurement data were expressed as means ± standard deviation ($x \pm s$), and the one-way analysis of variance was used for intergroup and intra-group comparisons. Two way ANOVA with repeated measures was applied to multiple measurements of incisional pain, uterine contraction pain/ and substance p. The least significant difference method was used for post hoc pairwise comparison. The chi-square test was used for countable data; $P < 0.05$ was considered statistically significant.

3. RESULTS

3.1 General Characteristics

The three groups were comparable with regard to maternal age, body mass index, gestational age, duration of surgery, the volume of intra-operative infusion, the number of cases of cardiovascular medications ,PCA bolus times and dezocine dosage for analgesia ($P > 0.05$). See Table 1.

3.2 Comparison of Postoperative Analgesic Effects among the Three Groups

3.2.1 Incisional pain at different postoperative times among the three groups

The two way ANOVA was used to compare the differeces of incisional pain among the three groups and the five time points. Comparcomparison between groups, F=10.141, P=0.000. It suggested that there was a statistical difference between groups; Time-point comparison, F=72.254, P=0.000, It suggested a statistical difference in the time point; FGroup *timepoint=3.027, P=0.003, It suggesed There was interaction between groups and Timepoits. Post-poc analysis, Incisional pain at whole time-points in Group PMD were lower than those in Group PD and Group MD（P=0.014,0.044, All P < 0.05).

Table 1. Comparison of the general characteristics among the three groups of puerpera (x ±s)

Group	Case	Age	Body mass index	Gestational age	Operation duration	Volume of intraoperative infusion	Cases with cardiovascular medication (Number of cases)			PCA bolus	Dezocine dosage
		(Year)	kg/m^2	Week	min	ml	Phenylephrine	Ephedrine	Atropine	Times	(mg)
The MD group	30	29.67±4.50	27.80±3.38	38.81±1.05	73.83±15.29	1175.00±287.30	14	16	7	6.45±1.35	33.24±5.62
The PD group	30	28.50±9.63	26.70±3.88	38.65±1.61	72.33±18.09	1283.33±313.03	12	18	5	6.04±1.65	34.62±6.34
The PMD group	30	30.67±4.05	28.13±2.40	38.93±1.20	73.67±15.64	1200.00±249.14	15	15	6	5.68±1.02	32.65±5.06
F (χ^2)		0.818	1.57	0.35	0.08	1.19	0.92			2.392	0.945
P		0.445	0.21	0.71	0.93	0.31	0.92			0.098	0.393

Table 2. Comparison of the VAS of incisional pain at different postoperative time points among three groups of puerpera (x ±s)

Item	Case	Group	2h postoperation	8h postoperation	12h postoperation	24h postoperation	48h postoperation
The incisional pain	30	The MD group	0.37±0.56	1.67±0.96	1.93±0.69	1.83±0.70	1.77±0.63
	30	The PD group	0.40±0.50	1.97±0.76**a**	2.60±1.22**a**	2.20±0.89	1.80±0.55
	30	The PMD group	0.30±0.50	1.17±0.79**ab**	1.63±1.00**b**	1.87±0.77	1.77±0.73
F			0.29	6.92	5.00	1.83	0.02
P			0.75	0.001	0.00	1.12	0.98

VAS of incisional pain at *2h postoperation:F=0.29，P=0.75，There were no statistical differences between the three groups.MD group vs PD，P=0.80; MD group vs PMD group，P=0.613；PD group vs PMD group，P=0.448.*

VAS of incisional pain at *8h postoperation:F=6.92，P=0.001，The three groups were statistically different;MD group vs PD，P=0.172; MD group vs PMD group，P=0.024；PD group vs PMD group，P=0.00.*

AS of incisional pain at 12*h postoperation:F=5.00，P=0.00，The three groups were statistically different;MD group vs PD, P=0.01; MD group vs PMD group，P=0.25；PD group vs PMD group ,P=0.00.*

AS of incisional pain at 24 *h postoperation: F=1.83，P=1.12，There were no statistical differences between the three groups.MD group vs PD，P=0.076; MD group vs PMD group，P=0.871；PD group vs PMD group，P=0.106.*

AS of incisional pain at 48 *h postoperation:MD group vs PD, F=0.02，P=0.98，There were no statistical differences between the three groups.MD group vs PD，P=0.84; MD group vs PMD group，P=1.00；PD group vs PMD group，P=0.840.*

Note: ***a*** *Compared with the MD group，P<0.05;* ***b*** *Compared with the PD group, P<0.05;*

Table 3. Comparison of the VAS of uterine contraction pain at different postoperative time points among three groups of puerpera (x ±s)

Item	Case	Group	2h postoperation	8h postoperationy	12h postoperation	24h postoperation	48h postoperation
The uterine contraction pain	30	The MD group	0.27±0.58	2.01±1.11	2.10±0.96	1.80±1.0	1.50±1.04
	30	The PD group	0.30±0.47	1.70±1.06	1.80±1.16	1.87±1.0	1.57±0.68
	30	The PMD group	0.40±0.50	1.23±1.10**a**	1.90±1.0	1.70±0.95	1.53±1.04
F			0.52	3.89	0.61	0.23	0.04
P			0.60	0.02	0.55	0.80	0.96

VAS of uterine contraction pain at 2h postoperation:，F=0.52，P=0.60，There were no statistical differences between the three groups.MD group vs PD，P=0.804; MD group vs PMD group，P=0.322；PD group vs PMD group，P=0.457.

VAS of uterine contraction pain at 8 h postoperation:F=3.89，P=0.02，The three groups were statistically different：MD group vs PD,．P=0.20; MD group vs PMD group，P=0.03；PD group vs PMD group ,P=0.35.

VAS of uterine contraction pain at 12 h postoperation:F=0.61，P=0.55，There were no statistical differences between the three groups.MD group vs PD，P=0.267; MD group vs PMD group，P=0.459；PD group vs PMD group，P=0.711.

VAS of uterine contraction pain at 24 h postoperation: F=0.23,P=0.80,There were no statistical differences between the three groups.MD group vs PD，P=0.0.794; MD group vs PMD group，P=0.695；PD group vs PMD group，P=0.514.

VAS of uterine contraction pain at 48 h postoperation:F=0.04,P=0.96,There were no statistical differences between the three groups：MD group vs PD，P=0.783; MD group vs PMD group，P=0.891；PD group vs PMD group，P=0.891.

Note: a Compared with the MD group，P<0.05; b Compared with the PD group, P<0.05;

Table 4. Comparison of adverse reactions 48 hours after surgery among three groups of puerpera (Number of cases)

Group	Case	Excessive vaginal hemorrhage	Nausea and vomiting	Dizziness and lightheadedness	Skin pruritus	Urinary retention	Respiratory depression
The MD group	30	5	3	3	2	4	0
The PD group	30	4	5	3	5	3	0
The PMD group	30	4	4	4	4	5	0
X^2		0.18	0.58	0.23	1.45	0.55	
P		0.91	0.75	0.89	0.48	0.76	

Table 5. Comparison of postoperative maternal mobility and breastfeeding among three groups of puerpera (x ±s)

Group	Case	The time to ambulation (h)	The step counts within 2 days after surgery (step)	The time to breastfeeding initiation(h)	The times of breastfeeding within two days (Times)
The MD group	30	11.83±4.25	1486.20±242.76	2.53±0.74	12.63±1.67
The PD group	30	9.30±3.80**a**	1483.07±142.07	2.65±0.80	11.03±1.81**a**
The PMD group	30	8.60±2.33**a**	1867.13±308.46**a**	2.32±0.76	16.27±2.71**ab**
F		6.84	25.9	1.42	48.59
P		0.00	0.00	0.25	0.00

The time to ambulation：F=6.84，P=0.00，The three groups were statistically different：MD group vs PD，P=0.41; MD group vs PMD group，P=0.01；PD group vs PMD group ,P=0.15.
The step counts within 2 days after surgery：F=25.9，P=0.00，The three groups were statistically different：MD group vs PD, P=0.96; MD group vs PMD group，P=0.00；PD group vs PMD group ,P=0.00.
The time to breastfeeding initiation:：F=1.42，P=0.25，There were no statistical differences between the three groups：MD group vs PD，P=0.179; MD group vs PMD group，P=0.736；PD group vs PMD group ,P=0.094.
The times of breastfeeding within two days :F=48.59，P=0.00，The three groups were statistically different：MD group vs PD, P=0.004; MD group vs PMD group，P=0.00；PD group vs PMD group ,P=0.00.
*Note: **a** Compared with the MD group, P<0.05; **b** Compared with the PD group, P<0.05.*

Table 6. Comparison of the serum levels of substance P at different time points among three groups of puerpera (x ±s)

Item	Group	One day before surgery	At the end of surgery	One day after surgery	Two days after surgery
Substance P	The MD group	67.64±5.68	69.86±5.30	72.08±7.41	72.66±6.63
	The PD group	66.50±4.63	65.14±5.17**a**	72.98±7.23	73.07±6.48
	The PMD group	68.27±4.97	67.52±6.87	68.05±5.02**ab**	72.27±5.02
F		0.92	4.91	4.69	0.13
P		0.40	0.001	0.01	0.88

***Serum levels of substance P at o**ne day before surgery:F=0.92，P=0.40，There were no statistical differences between the three groups：MD group vs PD, P>0.392; MD group vs PMD group，P=0.635；PD group vs PMD group ,P=0.185.*
***Serum levels of substance P at** the end of surgery:F=4.91，P=0.001，The three groups were statistically different：MD group vs PD, P=0.002; MD group vs PMD group，P=0.124；PD group vs PMD group ,P=0.008.*
***Serum levels of substance P o**ne day after surgery:F=4.69，P=0.01，The three groups were statistically different：MD group vs PD, q=0.74 P=0.603; MD group vs PMD group，P=0.021；PD group vs PMD group ,P=0.005.*
***Serum levels of substance P** two day after surgery:F=0.13，P=0.88,There were no statistical differences between the three groups：MD group vs PD, P0.793; MD group vs PMD group，P=0.805；PD group vs PMD group ,P=0.611.*
*Note: **a** Compared with the MD group, P<0.05; **b** Compared with the PD group, P<0.05*

One way ANOVA was used for the incisional pain in the three groups at diffenant timepoints. The difference in the VAS of incisional pain 2 h after surgery was not statistically significant among the three groups ($P > 0.05$). The VAS score differences in incisional pain at 8 h after surgery were statistically significant ($P < 0.05$) among the three groups, with that in the PMD group being lower than in the PD and MD groups and that in the PD group being higher than in the MD group. The VAS score differences in incisional pain at 12 h after surgery were statistically significant ($P < 0.05$) among the three groups, with that in the PMD and MD groups being lower than in the PD group and that in the PMD group being lower than in the MD group; there were no statistically significant differences between the two groups. The VAS score differences in incisional pain at 24 h and 48 h after surgery were not statistically significant among the three groups ($P > 0.05$) (see Table 2).

3.2.2 Comparison of the visual analog score of uterine contraction pain at different postoperative times among three groups

The two way ANOVA was used to compare the differeces of uterine contraction pain among the three groups and the five timepoints. Comparcomparison among the three groups, F=4.035, P=0.035.It suggested that there was no statistical difference among the three groups; Time-point comparison, F=43.732, P=0.000, It suggested a statistical difference in the time point; F Group *timepoint=0.915, P=0.504. It suggesed there was no interaction between groups and Timepoints. Post-poc analysis; the uterine contraction at whole time-points in Group PMD were lower than those in Group PD and Group MD（P=0.014,0.044, All P < 0.05). One way ANOVA was used for the uterine contraction pain in the three groups at diffenant timepoints. The VAS score differences in uterine contraction pain at 2 h after surgery were not statistically significant among the three groups (P > 0.05). The VAS score differences in uterine contraction pain at 8 h post-surgery were statistically significant among the three groups (P < 0.05), with that in the PMD group being lower than in the MD and PD groups. The VAS score differences in uterine contraction pain at 12, 24, and 48 h post-surgery were not statistically significant among the three groups (P > 0.05) (see Table 3).

3.3 Comparison of Postoperative Adverse Reactions among the Three Groups

The differences in the number of cases with adverse reactions, including excessive vaginal hemorrhage, nausea and vomiting, dizziness and drowsiness, pruritus, urinary retention, and respiratory depression were not statistically significant among the three groups (P > 0.05) (see Table 4).

3.4 Comparison of Postoperative Maternal Mobility and Breastfeeding among the Three Groups

The differences in the time to ambulation were statistically significant among the three groups (P < 0.05), with that in the PMD group having been earlier than in the PD and MD groups. The differences in step count within two days post-surgery were statistically significant among the three groups (P < 0.05), with that in the PMD group having been higher than in the PD and MD groups. The differences in the time to breastfeeding initiation were not statistically significant among the three groups (P > 0.05). The differences in the number of breastfeeding times within two days after surgery were statistically significant among the three groups (P < 0.05), with that in the PMD group having been higher than in the PD and MD groups, and that in the MD group being higher than in the PD group (see Table 5).

3.5 The Perioperative Serum Levels of Substance P among the Three Groups

The two way ANOVA was used to compare the differeces of incisional pain among the three groups and the five timepoints. Comparcomparison between groups, F=2.152, P=0.118.It suggested that there was no statistical difference between groups; Time-point comparison, F=17.273, P=0.000, It suggested a statistical difference in the time point; FGroup *timepoint=3.82, P=0.006, It suggesed There was interaction between groups and Timepoits. Post-hoc analysis, The substance P at the end of surgery, one day and two days after surgery were high than that before surgery (P=.000,0.000,0.000.).

One way ANOVA was used for the uterine contraction pain in the three groups at diffenant

timepoints. One day before surgery, the serum levels of substance P were not statistically significant among the three groups ($P > 0.05$). Compared with the MD group, the serum levels of substance P at the end of surgery in the PD group were lower ($P < 0.05$). The differences in the serum levels of substance P one day after surgery were statistically significant among the three groups, with that in the PMD group being lower than in the PD and MD groups. The differences in the serum levels of substance P two days after surgery were not statistically significant among the three groups ($P > 0.05$) (see Table 6).

4. DISCUSSION

A cesarean section, like other surgeries, causes acute postoperative incisional pain due to tissue trauma incurred during the operation and because of local inflammatory response in the postoperative incision. Normal uterine contractions and the use of oxytocin after a cesarean section may produce uterine contraction pain [11]. In addition, postoperative breast tenderness, an indwelling catheter, and concerns about breastfeeding can aggravate the maternal pain experience [12]. The decreased mobility associated with the puerperium may also increase the risk of embolic disease. Adequate analgesia refers to pain relief that does not interfere with postoperative mobility and prevents the associated risks, preserves the maternal ability to provide care to the newborn in the immediate postpartum period, and avoids adverse effects on early communication between mother and baby [11,12].

The classic approach to providing analgesia after a cesarean section is the epidural application of a low concentration of a local anesthetic compound; this includes commonly used opioids, such as morphine, sufentanil, and hydromorphone [13-15]. in addition to the adoption of a model of PCA with or without background infusion. A large number of clinical practices have confirmed that the analgesic effect of this method is definite and has few critical adverse effects on the mother or the newborn. However, there are some limitations to epidural analgesics, such as numbness and weakness in the lower limbs; this can affect postoperative ambulation, poses a high incidence of urinary retention, the delayed recovery of anal venting, accidental dislodgement of the epidural catheter (resulting in analgesic failure after surgery), and difficulties related to postoperative care [16]. Additional complications that may arise include epidural hematoma, abscess, and unexpected total spinal anesthesia [17].

In recent years, intravenous PCA has been applied to cesarean delivery by an increasing number of researchers [18]. However, it has also been concluded that intravenous analgesia alone is correlated with high dosing and an increased risk of neonatal exposure to opioids, combined with poor analgesic effect, a high incidence of adverse reactions (such as nausea and vomiting, pruritus, urinary retention, and dizziness and drowsiness), and a high risk of respiratory depression [18]. Particularly in female patients, the incidence of nausea and vomiting in the delivery of intravenous PCA is higher due to the influence of sex hormones and endocrine changes [19].

Accordingly, the application of multimodal analgesia appears to be a developing trend [18]. The authors previously used a single-bolus epidural injection of 1.5 mg of morphine, combined with intravenous analgesia of 0.5 mg/kg of dezocine, [7] and a single intravenous injection of 40 mg of parecoxib sodium combined with intravenous analgesia of 0.5 mg/kg of dezocine, [8] respectively, and achieved several effects. However, these postoperative analgesia protocols were unsatisfactory (for uterine contraction pain in the former and incisional pain in the latter). This was confirmed by the results presented herein.

The present study found that the VAS scores of incisional and uterine contraction pain within 12 h after surgery were lower in patients who received the three units of multimodal analgesia (a single intravenous injection of 40 mg of parecoxib sodium, a single-bolus epidural injection of 1.5 mg of morphine, and intravenous PCA with 0.5 mg/kg of dezocine) than in those who received two units of multimodal analgesia. Further, there was no statistical difference in the number of cases of adverse reactions among the three groups, which tentatively confirmed the clinical value of the combined use of the three units of multimodal analgesia.

Parecoxib sodium is a selective cyclo-oxygenase-2 (COX-2) inhibitor that can effectively inhibit the peripheral expression of COX-2 and reduce the peripheral synthesis of prostaglandin, thereby exerting analgesic and anti-inflammatory effects. It can also inhibit the

central expression of COX-2 and the central synthesis of prostaglandin, exerting both peripheral and central analgesic advantages while inhibiting opioid-induced nociceptive hyperalgesia, with an analgesic duration of more than 6–12 h from a single dose [20,19,21]. Wong et al. [22] gave 40 mg of intravenous parecoxib sodium to women following cesarean delivery, followed by another parecoxib bolus (20 mg) every 24 h, in addition to using PCA with morphine; the study achieved a good analgesic effect and a decreased total morphine requirement (22% reduction) without significant adverse reactions. Paech et al. used an intravenous injection of 40 mg of parecoxib and an oral administration of 400 mg of celecoxib every 12 h with an epidural PCA in patients receiving pethidine. The results showed that, although the dosage of pethidine could not be reduced in the first 24 h, the amount of remedial analgesia with oral tramadol could be reduced [23].

Although all the above studies maintained the dosing of COX-2 inhibitors combined with intravenous analgesia only, the analgesic effects remained unsatisfactory and required remedial analgesic measures. Therefore, some researchers have combined parecoxib with intraspinal morphine for analgesia. Nittaya et al. [24] used a single intravenous injection of 40 mg of parecoxib with intrathecal morphine-assisted analgesia in women undergoing a cesarean delivery and found that parecoxib was inadequate for reducing the maternal need for pethidine supplementation after delivery. However, it did reduce pain scores and improved patient satisfaction and was associated with the suppression of uterine contraction pain [25]. A study conducted by Shen et al. [26] combined a single intravenous injection of 40 mg of parecoxib with a single-bolus epidural injection of 2 mg of morphine. The results showed that incisional and uterine contraction pain was reduced.

This study confirmed the value of combining parecoxib sodium with intrathecal or epidural morphine for postoperative analgesia after a cesarean section. Interestingly, the study used a single intravenous injection of parecoxib sodium that was not subsequently maintained with parecoxib sodium or celecoxib. This was due to the concern of transferring parecoxib sodium or celecoxib to the infant through breast milk. Later studies have confirmed the value of a single intravenous injection of parecoxib as postoperative analgesia following cesarean delivery [27,28–32].

It has been suggested that parecoxib sodium has a 98% plasma protein binding rate with a maternal/fetal (M/P) ratio of 0.18. It does not readily enter the breast milk and does not require cessation of breastfeeding with a single dose [33]. Therefore, a single intravenous injection of 40 mg of parecoxib is recommended as postoperative analgesia treatment following a cesarean delivery; however, there is no evidence that the continuous administration of parecoxib is required 24–48 h postoperatively.

However, the duration of observation in most studies was limited to 24 h postoperatively. In the present study, pain at 48 h postoperatively was observed. VAS score differences for incisional and uterine contraction pain at two time points (24 and 48 h postoperatively) were not statistically significant among the three groups. The action duration of a single intravenous injection of parecoxib is 8–12 h [21], and that of a single-bolus epidural injection of 1.5 mg of morphine is 10–17 h; [34] Therefore, the effects of parecoxib and morphine would have worn off during the 24–48 h postoperative period, at which time dezocine delivered via an intravenous analgesic pump took effect. Although we observed that the VAS scores for incisional pain and contraction pain were lower at 24–48 h postoperatively than at 6–12 h, this was due to the discontinuation of oxytocin and the recovery of maternal strength and mood, resulting in lower VAS scores.

For pain-sensitive women, analgesia may be required for up to 48 h post-surgery to address the limited duration of action of a single-bolus epidural injection of morphine, Fonseca et al. [3] retained an epidural catheter after an injection of 1.5 mg of morphine, and 1.5 mg of morphine was re-injected via epidural at 24 h postoperatively. Although only one unit of analgesic mode was conducted in this particular study, the results revealed a significant reduction in pain in the 24–48-h postoperative period. They were comparable to the effect of epidural opioids combined with low concentrations of local anesthetics. It was concluded that the latter could increase the incidence of adverse reactions (e.g., lower extremity numbness) and were thus unnecessary. As noted above, due to concerns about neonatal drug exposure [33] and the fact that parecoxib administration in breastfeeding mothers is considered an off-label medication,

[21] its continuous administration (or drugs similar to it) is not recommended. A second epidural injection of morphine may be given to improve analgesia in the 24–48 h postoperative period, as demonstrated by Fonseca et al. [3].

The present study also found that the combined application of the three units of multimodal analgesia was more effective and did not increase the incidence of adverse reactions, resulting in earlier postoperative ambulation than the patients in the other two groups. The step counts (measured using pedometer software installed on the participant's cellphone) in the multimodal analgesia group were also significantly higher than the other two groups. It has been confirmed that good analgesia and early ambulation may promote maternal milk production [34]. The findings in the present study also verified that although there was no statistical difference in the time to breastfeeding initiation among the three groups, the number of times breastfeeding occurred among the women who received the three units of multimodal analgesia was significantly higher than in the other two groups. Meanwhile, early ambulation may reduce the risk of puerperal infections and thrombotic events [35].

Substance P is a neuropeptide comprising 11-amino acid, an undecapeptide that belongs to the tachykinin neuropeptide family. Its receptor, neurokinin type 1, is a trans-membrane binding receptor found on many cells in the body, including vascular endothelium and lymphatic vessels, white blood cells, fibroblasts, and neurons [36]. Substance P is best known for functioning as a neurotransmitter and modulator of pain perception by altering cellular signaling pathways [36]. The present study found that the serum levels of substance P at the end of the surgery, as well as one day after surgery, were lower in women who received parecoxib than in those who did not. Furthermore, participants who received the three units of multimodal analgesia had significantly lower substance P levels compared to participants in the other two groups, suggesting that parecoxib could significantly inhibit the serum levels of substance P. Since substance P is a pain mediator, [36] the analgesic effect of parecoxib was suggested as possibly being related to the inhibition of the release of substance P. Yu et al. demonstrated that pretreatment with an intravenous injection of parecoxib sodium could effectively inhibit the release of intraoperative and postoperative substance P levels during a cesarean delivery, which may be beneficial to maternal health [31,32]. However, the present study revealed that differences in the serum levels of substance P at two days post-surgery were not statistically significant among the three groups, suggesting that the level of substance P may be related to the degree of maternal pain, as there were no statistically significant differences among the three groups concerning pain scores at 24–48 h post-surgery. Since substance P is also a key molecule in the neurogenic inflammatory response, it acts as a molecule that plays a critical role in the interaction between the nervous and immune systems [36]. The effects of parecoxib on other stress and immune factors were investigated in other studies, and it was found that parecoxib could also reduce serum levels of interleukin 6, tumor necrosis factor alpha, C-reactive protein, and cortisol [30-32]. These results further confirmed that parecoxib may inhibit inflammation and stress following a cesarean section and facilitate maternal recovery.

5. CONCLUSION

In conclusion, The single intravenous sodium parecoxib combined with single epidural morphine and dezocine intravenous analgesia can better reduce the incision pain and uterine contractile pain after cesarean section, promote maternal postoperative off-bed activity and breast-feeding times to newborn.

The limitations in the present study were the following: (1) The number of maternal cases in the current research was limited; its conclusions should thus be validated in a multicenter study with more cases. (2) Due to the limited number of cases in the present study, no specific incidence of adverse reactions could be derived; further studies with a large sample size are thus needed to draw conclusions in this context. (3) Further confirmation of postoperative maternal mobility and breastfeeding is needed by conducting well-designed studies. (4) Only the serum level of substance P was investigated in the present study; additional research is needed regarding the levels of substance P in the spinal cord and other areas of the nervous system.(5) In our study, there was no significant effect on pain or the release of substance P at 24 h after surgery. New methods should be investigated for improving analgesia 24 h after surgery.

FUNDING

Science and Technology Innovation Project of Foshan (No.2020001005655).

CONSENT AND ETHICAL APPROVAL

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The Second People's Hospital of Foshan (KJ2020030).A written informed consent was obtained from all participants

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/103079