

Impact of Intraoperative Infusion and Postoperative PCIA of Dexmedetomidine on Early Breastfeeding After Elective Cesarean Section: A Randomized Double-Blind Controlled Trial

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Objective: Few studies have investigated the effects of dexmedetomidine (DEX) on breastfeeding after cesarean delivery. A randomized double-blind controlled trial was conducted to investigate whether the administration of DEX, immediately after delivery and for patient-controlled intravenous analgesia (PCIA), can be beneficial for breastfeeding.

Patients and Methods: One hundred sixty parturients scheduled for elective cesarean section under spinal anesthesia were randomly allocated to the DEX group (a loading dose of DEX was pumped at 0.5 µg/kg within 10 min, followed by a further infusion of DEX at 0.5 µg/kg/h until the end of the surgery and PCIA for 2 days with DEX plus sufentanil) or the standard care group (infusion saline intraoperatively, and PCIA for 2 days with sufentanil). The number of days required to switch to exclusive breastfeeding within six weeks of delivery, the time to first lactation and breast milk volume on day 1 and day 2 after delivery were recorded. Recovery quality, comfort, anxiety, depression, postoperative analgesia, and adverse reactions of parturients were also assessed.

Results: Compared with the standard care group, parturients in the DEX group could be converted to exclusive breastfeeding earlier (11 [14] vs 8 [10] days, log-rank $P=0.025$), the first lactation time was sooner (28.38 [13.82] vs 33.79 [14.85] hrs, $P=0.024$), and the amount of breast milk on the second day after delivery increased ($P=0.012$). There was no difference between the two groups in postpartum uterine contraction pain, but postpartum rest and movement VAS scores and recovery quality score in the DEX group were better than those in the standard care group (all $P<0.05$). Moreover, the hospital anxiety and depression scale and anxiety subscale score on the second day after delivery and the comfort score on the third day after delivery in the DEX group were significantly better than those in the standard care group (5 [5] vs 6 [8], 2 [2] vs 3 [3], 83.58 [6.75] vs 80.48 [6.58]; $P=0.013$, $P=0.005$, $P=0.006$, respectively). The incidence of adverse events, such as bradycardia, vomiting, hypersomnia, hypertension and hypotension, was not significantly different between the DEX and standard care groups (6.9% vs 2.7%, 5.6% vs 13.7%, 4.2% vs 0%, 5.6% vs 2.7%, 11.1% vs 8.2%; $P=0.275$, $P=0.158$, $P=0.366$, $P=0.681$, $P=0.556$, respectively), except more parturients experienced nausea in the standard care group than in the DEX group (28.8% vs 11.1%, $P=0.012$). Furthermore, there was no difference in Neonatal Behavioral Neurological Assessment scores on the first and second days after delivery between the DEX and standard care groups (38 [3] vs 37 [2], 38.5 [2] vs 38 [2]; $P=0.173$, $P=0.312$, respectively).

Conclusion: The application of DEX in the perioperative period of cesarean section was not only conducive to the early conversion of infant feeding to exclusive breastfeeding but could also improve the recovery quality and comfort of the parturient, optimize analgesia, shorten the time to first lactation, and increase lactation.

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Introduction

Breastfeeding is an important means for human beings to survive and multiply. The American Academy of Pediatrics recommends that all infants should be exclusively breastfed for the first 6 months,¹ and early breastfeeding has significant short-term and long-term benefits for both mothers and infants,^{2,3} while in China, only approximately 21% of infants are exclusively breastfed for up to 6 months.⁴ The initiation and maintenance of breast milk secretion is mainly dependent on the sucking stimulation of the baby and the synergy between prolactin and oxytocin. Nevertheless, inadequate breast milk supply and maternal loss of feeding initiative due to pain, poor perinatal mood or even work can delay early breastfeeding.⁵⁻⁷ Despite perinatal support such as home care, gynecologists, nurses and lactation consultants, the early stages of breastfeeding are still much more difficult than previously thought.

The incidence of postoperative incision pain, pain of scar contracture of the uterus and anxiety and depression caused by cesarean section was higher than that among women who experienced vaginal delivery. Stress caused by these factors can increase the release of dopamine and dynorphin in the body and inhibit the secretion and release of prolactin and oxytocin, thereby reducing the secretion of breast milk.^{8,9} This can cause maternal loss of breastfeeding initiative and reduce infant sucking. Previous studies have revealed that planned cesarean section is associated with early breastfeeding cessation compared with breastfeeding cessation associated with vaginal delivery.¹⁰

Dexmedetomidine (DEX) is an adrenergic alpha 2 receptor agonist with both analgesic and sedative effects. DEX can produce an analgesic effect by inhibiting the release of damage-transmitting substances such as substance P and glutamate and activating spinal dorsal horn neurons to suppress pain signaling.^{11,12} Recent studies have confirmed that DEX can be used in the perioperative period of cesarean section to assist analgesia.^{13,14} There are also studies reporting the effect of DEX on improving mood.^{15,16} Furthermore, it is worth mentioning that DEX can act on the locus coeruleus and thus produce a sedative effect similar to natural sleep by activating endogenous

sleep pathways.^{17,18} This effect may be helpful for parturient women to avoid various perioperative stresses and improve perioperative comfort without the risk of respiratory depression. However, it is unclear whether these advantages of DEX can have benefits in the context of maternal breastfeeding. We hypothesized that intraoperative infusion and postoperative PCIA of dexmedetomidine would allow parturients to switch to exclusive breastfeeding earlier and improve breastfeeding outcomes.

Subjects and Methods

Study Design

This single-center, prospective, randomized, double-blinded, parallel, controlled trial was conducted at a tertiary university teaching hospital in China from June 2019 to December 2019. The study protocol was approved by the clinical research ethics committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2019-KL054-02). This trial was registered at ClinicalTrials.gov (NCT03805945). All study participants read and signed informed consent forms. This trial was conducted in accordance with the Declaration of Helsinki.

Eligibility Criteria

The inclusion criteria included (1) American Society of Anesthesiologists physical status II; (2) aged 20–40 years; (3) 37–42 weeks of pregnancy; (4) body mass index ≤ 35 kg/m²; and (5) willingness to breastfeed and expect exclusive breastfeeding for more than three months. Parturients were excluded if they met any of the following criteria: (1) emergency cesarean section; (2) contraindications for spinal anesthesia (abnormal coagulation, lumbar disc herniation, spine deformity or history of surgery); (3) twin pregnancy; (4) allergy to α_2 -adrenergic agonist or opioids; (5) use of analgesics or sedatives before surgery; (6) inability to understand the various scales used in this trial; (7) neurological or psychiatric diseases; or (8) inclusion in other clinical trials.

Randomization, Blinding, and Allocation Concealment

Participants were randomly assigned to the DEX group or the standard care group using a computer-generated 1:1 random

number table. The randomization table was kept in the anesthesiology pharmacy where study medication and patient-controlled intravenous analgesia (PCIA) solutions were prepared. Researchers who performed data collection, postpartum follow-up, and statistical analysis and subjects were blinded throughout this trial. In case of any emergency that endangered the parturient or the newborn, the study allocation would be unmasked to ensure maternal and infant safety.

Anesthesia Procedures

All pregnant women aged 20–40 years with a term pregnancy who planned elective cesarean section were consecutively screened for eligibility one day before operation and were then recruited if parturients were willing to sign the consent form. Prior to spinal anesthesia, participants were given 300–400 mL of compound electrolyte solution, and the following parameters were monitored for all parturients: heart rate, electrocardiogram (ECG), noninvasive blood pressure (NIBP) and pulse oximetry (SpO₂). The follow-up staff used a preoperative questionnaire form to collect basic information on all participants, including age, height, weight, gestational age, whether or not primipara, scar uterus status, education.

According to the discretion of the anesthesiologist, subarachnoid puncture was performed in the parturient L₃₋₄ space under sterile conditions using a 25G lumbar anesthesia needle. According to their height, all parturient women were treated with 7.5–12 mg of 0.5% bupivacaine diluted with cerebrospinal fluid. After the lumbar anesthesia needle entered the subarachnoid space, the smooth flow of cerebrospinal fluid was confirmed and then the drug solution was injected at a rate of approximately 0.1 mL/s. After completion of spinal anesthesia, which was performed by an attending anesthesiologist who did not participate in data collection or analysis, the parturient turned from the left lateral position to the supine position, and an oxygen mask at a flow rate of 5 L/min was used. After the subarachnoid block was completed, the sensory block plane was maintained at the T4-6 level.

Study Interventions

The drug interventions accepted by all participants in the study were as follows: DEX group: After the umbilical cord was cut, a loading dose of DEX was pumped at 0.5 µg/kg within 10 min, followed by a further infusion of DEX at 0.5 µg/kg/h until the end of the surgery. Then, the patients were connected to a PCIA pump. The PCIA protocol: DEX 2 µg/kg + sufentanil 1.5 µg/kg + dolasetron 25 mg. The standard

care group was treated as follows: After the umbilical cord was cut, the same amount of saline was injected at the same rate during the same time period as that of the DEX group. Then, they were connected to a PCIA pump. The PCIA protocol was as follows: sufentanil 1.5 µg/kg + dolasetron 25 mg. The PCIA parameters were as follows: total amount 100 mL, background infusion rate 2 mL/h, and bolus dose 0.5 mL, with a lock-out of 15 min. The unlabeled study drug was configured by an anesthesia nurse who was not involved in this trial and who provided the drug to clinical anesthesia practitioners.

Outcomes and Measurements

Our primary outcome measure was the number of days needed to convert infant feeding to exclusive breastfeeding within 6 weeks of delivery. Follow-up was carried out once a day until the sixth week after delivery.

Secondary outcomes included the first lactation time and milk volume on the first and second days after delivery. Breast milk volume grading was set by the experimental researcher as follows: I, no milk was produced; II, breast milk cannot meet the feeding needs of newborns; III, breast milk can meet the feeding needs of newborns; and IV, there is breast milk surplus after feeding the newborn. Moreover, we used the Hospital Anxiety and Depression Scale (HADS)¹⁹ and obstetric quality-of-recovery score (ObsQoR-11)²⁰ to measure baseline characteristics and changes in maternal mood and recovery quality before surgery and on days 1 and 2 after surgery. We also measured the General Comfort Questionnaire (GCQ)²¹ on the third day after delivery to assess comfort during the hospital stay. The HADS is divided into two subscales: anxiety and depression (≥8 points considered positive), and the higher ObsQoR-11 (a full score of 110) and GCQ (a full score of 112) scores represent higher maternal recovery quality and comfort. Pain was divided into three types: resting pain, movement pain and uterine contraction pain, and pain was assessed at 6, 12, 24, and 48 hrs after surgery using the visual analogue scale (VAS) (a 10-point scale where 0 indicated no pain and 10 indicated the worst possible pain).

Additional outcomes included a neonatal behavioral neurological assessment (NBNA)²² on days 1 and 2 postpartum and neonatal 1-min and 5-min Apgar scores. The NBNA is a score widely used in China to evaluate neonatal behavioral nerve function. The NBNA is divided into 20 items, each item receiving 0, 1, 2 points according to different degrees, with a full score out of 40 points. The

higher the score, the better the neonatal behavioral nerve function. Exhaust time (defined as the time from the end of the surgery to the occurrence of flatulence) was also recorded. Adverse reactions such as bradycardia (heart rate < 40 beats/minute), nausea, vomiting, hypersomnia, hypertension (systolic blood pressure > 180 mmHg or blood pressure over 30% of baseline) and hypotension (systolic blood pressure < 90 mmHg blood pressure is less than 30% of baseline blood pressure) within 48 hrs after delivery were also recorded. Follow-up during hospitalization was carried out by the follow-up personnel entering the ward. After discharge, follow-up was conducted by telephone and WeChat (a kind of instant messaging software).

We set up a contingency plan. If tachycardia (heart rate > 100 beats/minute) and hypertension occurred during the procedure, we discontinued the trial drug and fluid infusion and used the appropriate drug at the discretion of the anesthesiologist in charge at the time. Similarly, if bradycardia or hypotension occurred, we discontinued the trial drug, sped up the fluid infusion, and decided whether to use vasoactive drugs according to the anesthesiologist's judgment.

Statistical Analysis

The sample size calculation was based on the primary outcome. According to previous research data, the exclusive breastfeeding rate is approximately 70% at 6 weeks postpartum.²³ Assuming that the exclusive breastfeeding rate of the standard care group would be similar to that in previous studies, we expected the DEX group to improve by 15%. Using the PASS 15.0 software (NCSS, LLC, Kaysville, USA), based on a two-sided test of the Log-rank test module with a power of 80%, a significance level of 0.05 and a 15% loss rate, the total sample size was calculated to be 159 (80 in the DEX group and 79 in the standard care group). A total of 160 participants were finally included, with 80 in each group.

For numeric variables, the Kolmogorov–Smirnov test was used to verify normality. Normally distributed variables are expressed as the mean (SD), and abnormally distributed variables are expressed using the median (interquartile range). Categorical variables are expressed as numbers (percentages). Independent two-sample t-tests were used to compare normally distributed variables. Abnormally distributed variables and ranked data were compared using the Mann–Whitney *U*-test. Categorical variables were analyzed using the χ^2 test or Fisher's exact test. Kaplan–Meier curves were plotted for early exclusive breastfeeding and compared by

the Log-rank test and Cox model. According to whether the data were normally distributed, the differences between the two groups in repeated measurement data were analyzed by two-way repeated measures ANOVA or generalized estimating equations. The Bonferroni correction was used for post hoc analysis in terms of the number of comparisons. Data were analyzed using SPSS (version 24.0; SPSS Inc., IBM, Chicago, IL, USA). All statistical tests were two-tailed, and a P-value less than 0.05 was defined as statistically significant.

Results

From June 2019 to October 2019, we screened 271 parturients who had planned elective cesarean section. According to the inclusion and exclusion criteria and the voluntary principle, 160 pregnant women were included and randomly assigned to the DEX group or the standard care group. During the follow-up period, 10 participants (5 per group) were excluded from the analysis because they discontinued PCIA early for various reasons within 2 days after delivery, and 5 participants (3 participants in the DEX group and 2 participants in the standard care group) were excluded because the newborn was transferred to the neonatal intensive care unit after delivery. Eventually, 72 parturients who were included in the DEX group and 73 parturients who were included in the standard care group entered the analysis stage. The complete flow chart of participant selection in this study can be seen in [Figure 1](#).

Demographic Characteristics

There were no significant differences in demographic variables between the two groups, except that the gestational age was lower in the standard care group than in the DEX group ($P=0.038$). The duration of surgery and delivery, the weight and sex of newborns, and the Apgar score of newborns were not significantly different ([Table 1](#)).

Primary Outcome

Parturients in the DEX group could be converted to exclusive breastfeeding earlier than those in the standard care group (log-rank $P=0.025$) ([Figure 2](#)). Furthermore, we used the Cox regression model to further analyze our primary outcome. The univariate Cox regression hazard ratio (95% CI) for exclusive breastfeeding was 1.515 (1.037, 2.214) ($P=0.032$), indicating that the probability of converting to exclusive breastfeeding within 6 weeks postpartum in the DEX group was 1.515-times higher than that in the standard care group. Combined with the results

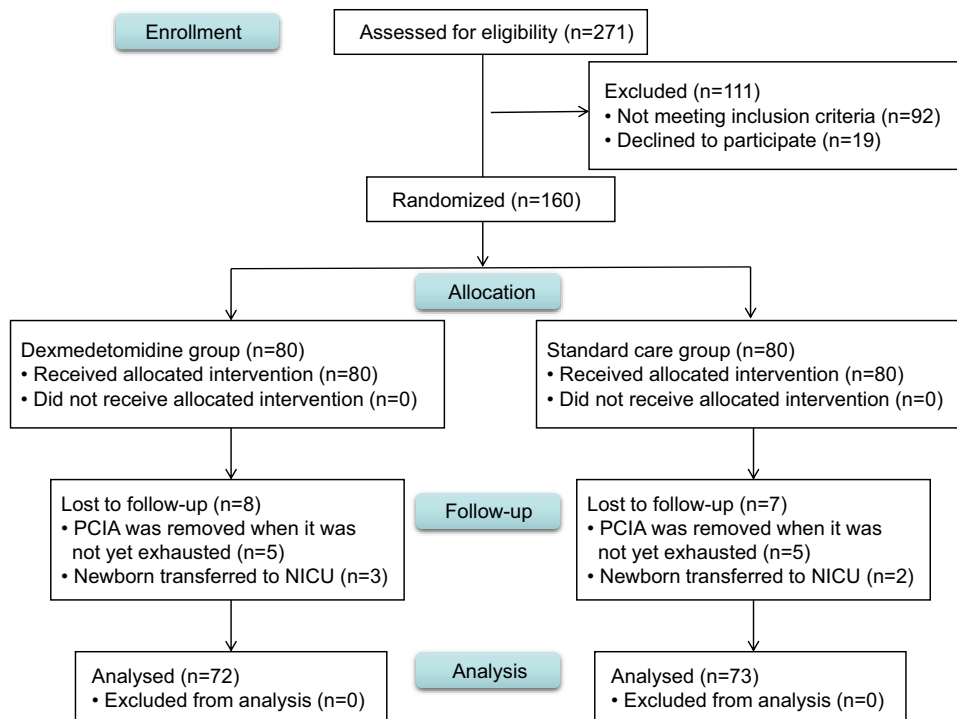


Figure 1 Flow diagram based on CONSORT statement.

of univariate analysis and clinical considerations, we included grouping, gestational age, educational attainment, multipara status, and neonatal gender in the multivariate

Cox regression analysis. After multivariate correction, the adjusted hazard ratio (95% CI) was calculated to be 1.739 (1.168, 2.588) ($P=0.006$), indicating that the probability of

Table 1 Demographic Characteristics

Variable	Dexmedetomidine Group (n =72)	Standard Care Group (n =73)	P-value
Age (y), mean (SD)	30.72 (4.18)	31.10 (3.60)	0.565
Height (cm), mean (SD)	163.03 (5.83)	163 (5.34)	0.976
Weight (kg), mean (SD)	73.32 (7.42)	74.53 (7.25)	0.32
BMI, mean (SD)	27.62 (2.74)	28.08 (2.71)	0.301
Education attainment, no. (%)			0.225
Junior high school or under	17 (23.6)	10 (13.7)	
High school	13 (18.1)	19 (26.0)	
College or above	42 (58.3)	44 (60.3)	
Gestational age (weeks), mean (SD)	39.34 (0.97)	39.03 (0.79)	0.038
Multipara (yes/no)	50/23	51/21	0.759
Scar uterus (yes/no)	45/28	47/25	0.65
The duration of surgery (min), mean (SD)	63.61 (12.14)	61.68 (11.45)	0.327
The duration of delivery to the end of surgery (min), mean (SD)	55.88 (11.36)	55.40 (10.78)	0.795
Neonatal gender (male/female)	45/28	42/30	0.684
Neonatal weight (g), mean (SD)	3458.89 (295.85)	3413.56 (336.64)	0.391
1min Apgar score, median (IQR)	9 (1)	9 (1)	0.653
5min Apgar score, median (IQR)	10 (1)	10 (1)	0.53

Notes: Data are presented as mean (SD), median (IQR), or number (%). Significant differences are at $P<0.05$.

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Scar uterus, refers to a uterus that has undergone a cesarean section.

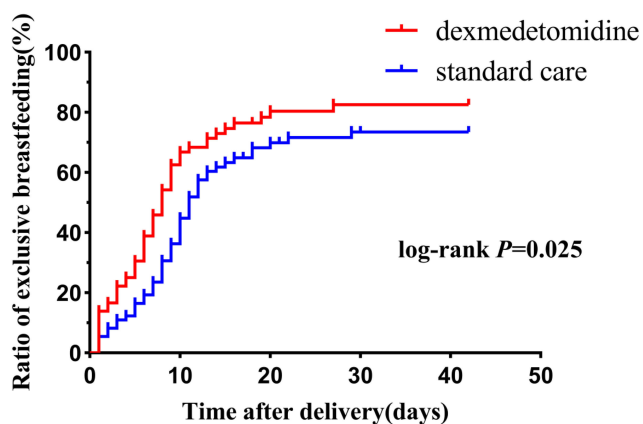


Figure 2 Kaplan-Meier curves for ratio of exclusive breastfeeding after delivery between the two groups.

exclusive breastfeeding within 6 weeks postpartum in the DEX group was 1.739-times higher than that in the standard care group.

Secondary Outcomes

The DEX group had shorter time to first lactation than the standard care group ($P=0.024$). The milk volume in the standard care group was less than that in the DEX group on the second postpartum day ($P=0.012$), but there was no significant difference between the two groups on the first postpartum day (Table 2).

Table 2 First Lactation Time and Milk Volume

Variable	Dexmedetomidine Group (n =72)	Standard Care Group (n =73)	P-value
First lactation time (min), mean (SD)	28.38 (13.82)	33.79 (14.85)	0.024 [#]
Milk volume on the day 1 postpartum (%)			0.131
I	44 (61.1)	55 (75.3)	
II	22 (30.6)	16 (21.9)	
III	6 (8.3)	2 (2.7)	
Milk volume on the day 2 postpartum (%)			0.015 [#]
I	9 (12.5)	25 (34.2)	
II	41 (56.9)	31 (42.5)	
III	14 (19.4)	13 (17.8)	
IV	8 (11.1)	4 (5.5)	

Notes: Data are presented as mean (SD), or number (%). [#]Significant differences are at $P<0.05$.

Abbreviation: SD, standard deviation.

The repeated measurement data of recovery quality at multiple time points and of the comfort of the third day after delivery were significantly higher in the DEX group than in the standard care group (all $P<0.05$). In the post hoc analysis of the quality of recovery on the first and second days after delivery, the DEX group was also superior to the standard care group (all $P<0.017$). There was no significant difference in the HADS scores between the two groups in the comparison of repeated measurement data at multiple time points ($P=0.096$). However, post hoc analysis showed that the second day of postpartum HADS scores and the anxiety subscale scores of the DEX group were better than those of the standard care group (all $P<0.017$) (Table 3).

When the repeated measurements of rest and movement VAS scores were compared at multiple time points, the DEX group exhibited lower scores than the standard care group (all $P<0.05$). In the post hoc analysis, the DEX group had lower VAS pain scores than the standard care group at 6 and 12 hrs of rest after delivery (all $P<0.0125$); the VAS pain scores with 12 hrs of movement were lower in the DEX group than in the standard care group after delivery ($P=0.002$). There was no significant difference between the groups at other time points (all $P>0.0125$) (Table 4).

Additional Outcomes

Additional outcomes are reported in Table 5. The incidence of nausea in the DEX group was lower than that in the standard care group ($P=0.012$), and the exhaust time was also shorter than that in the standard care group ($P=0.044$). The incidence rates of bradycardia, vomiting, hypersomnia, hypertension and hypotension were not significantly different between the two groups (all $P>0.05$). Furthermore, there was no significant difference in NBNA scores on the first and second days after delivery (all $P>0.05$), suggesting that DEX was not harmful to newborns.

Discussion

The results of the current study showed that parturients in the DEX group could be converted to exclusive breastfeeding more quickly within 6 weeks, the first lactation time could be shortened, and the amount of breast milk in the DEX group on the second day after delivery increased compared with that in the standard care group. In addition, maternal recovery quality, comfort, and postpartum pain were better in the DEX group than in the standard care group. Moreover, there was no significant difference in adverse reactions between the two groups.

Table 3 Maternal Recovery Quality, Comfort, Anxiety and Depression

Variable	Dexmedetomidine Group (n =72)	Standard Care Group (n =73)	P-value
ObsQoR-II, mean (SD), score			<0.001 [#]
Preoperative	98.08 (3.70)	98.16 (3.92)	0.898
1st day after delivery	73.14 (12.25)	66.67 (11.58)	0.001*
2nd day after delivery	88.74 (7.44)	84.67 (8.37)	0.002*
HADS, median (IQR), score			
Total score			0.061
Preoperative	8.5 (7)	8 (6)	0.733
1st day after delivery	7 (6)	8 (6)	0.078
2nd day after delivery	5 (5)	6 (8)	0.013*
Anxiety subscale			0.06
Preoperative	5 (3)	5 (3)	0.8
1st day after delivery	4 (3)	5 (4)	0.085
2nd day after delivery	2 (2)	3 (3)	0.005*
Depression subscale			0.107
Preoperative	2 (3)	2 (3)	0.99
1st day after delivery	3 (4)	4 (5)	0.084
2nd day after delivery	2 (3)	3 (4)	0.07
GCQ on the 3rd day after delivery, mean (SD), score	83.58 (6.75)	80.48 (6.58)	0.006 [#]

Notes: Data are presented as mean (SD), or median (IQR). [#]Significant differences are at P<0.05; *Significant differences are at P<0.017.

Abbreviations: SD, standard deviation; IQR, interquartile range; ObsQoR-II, obstetric quality-of-recovery score; HADS, Hospital Anxiety and Depression Scale; GCQ, General Comfort Questionnaire.

Without considering the censored data, the exclusive breastfeeding rate at 6 weeks postpartum in this study was 57 of 65 parturients (87.7%) in the DEX group and 51 of 65 parturients (78.5%) in the standard care group. Due to the existence of surgical factors, compared with labor analgesia, cesarean section is inevitably associated with more severe postpartum pain and negative emotions caused by pain, all of which can lead to weak positivity for breastfeeding. According to the results of the survival analysis of this study, it was found that the application of DEX in the perioperative period of cesarean section could result in conversion to exclusive breastfeeding earlier. For parturients who could not receive labor analgesia, this degree of early breastfeeding improvement was indeed very rare. In addition, DEX can shorten the time to first lactation and increase milk secretion, which provides the foundation for the early establishment of exclusive breastfeeding.

In our study, during the operation, DEX infusion after umbilical cord cutting could have caused maternal sleep and reduce the discomfort caused by intraoperative stimulation. DEX combined with sufentanil assisted analgesia after surgery, which could also reduce resting

pain and exercise pain. Consistent with the study of DEX in other populations,²⁴ the perinatal experience, such as maternal recovery quality and comfort, in the DEX group was also improved compared to that in the standard care group. These benefits increase maternal motivation to breastfeed, increase the number of times the baby sucked on the nipple, and then increase the pituitary reflex secretion of prolactin and the release of oxytocin. Other studies have shown that²⁵ DEX can reduce the release of inflammatory factors and reduce sympathetic activity, which explains why the exhaust time of the maternal DEX group is shorter than that of the standard care group. The shortened exhaust time will make the mothers eat earlier than those in the standard care group, which is conducive to improving the nutritional status of the mother and increasing lactation. In addition, Yu et al¹⁶ used almost the same intervention method and drug dose as those used in this trial, showing that DEX in the early postpartum period significantly reduced the incidence of postpartum depression within 7 days and 42 days. Early postpartum depression can lead to the interruption or abandonment of exclusive breastfeeding,^{26,27} which means that DEX can improve

Table 4 Pain at Rest, During Movement, and Secondary to Uterine Contractions Up to 48 hrs After Delivery

VAS Scores	Dexmedetomidine Group (n =72)	Standard Care Group (n =73)	P-value
VAS for rest pain, median (IQR), score			<0.001 [#]
6 hrs after delivery	3 (2)	4 (2)	0.001 ^Δ
12 hrs after delivery	2.5 (1)	3 (1)	0.002 ^Δ
24 hrs after delivery	2 (1)	2 (2)	0.019
48 hrs after delivery	1 (1)	1 (2)	0.465
VAS for movement pain, median (IQR), score			0.013 [#]
6 hrs after delivery	5 (2)	6 (3)	0.029
12 hrs after delivery	3 (1)	4 (1)	0.002 ^Δ
24 hrs after delivery	3 (2)	3 (1)	0.045
48 hrs after delivery	2 (1)	2 (1)	0.353
VAS for uterine contraction pain, median (IQR), score			0.054
6 hrs after delivery	4 (3)	5 (2)	0.032
12 hrs after delivery	3 (1)	3 (1)	0.122
24 hrs after delivery	3 (2)	3 (2)	0.246
48 hrs after delivery	2 (1)	2 (2)	0.502

Notes: Data are presented as median (IQR). [#]Significant differences are at P<0.05; ^ΔSignificant differences are at P<0.0125.

Abbreviations: IQR, interquartile range; VAS, Visual Analogue Scale.

early breastfeeding by reducing the incidence of postpartum depression.

Compared with the study done by Yu et al¹⁶, in the present study, although the HADS scores and anxiety subscale scores on day 2 postpartum were better in the DEX group than in the standard care group, there was a lack of difference in the overall comparison of repeated measurement data between the two groups. On the one hand, this may be because the sample size of this study was calculated based on the primary outcome, so the sample size may have been relatively insufficient to compare the difference in HADS between groups. On the other hand, it may also be because the pain is strong on the first and second days after delivery, and the maternal experience of negative emotions such as anxiety and depression is still not obvious, which masks the possible differences.

Consistent with a previous meta-analysis²⁸ that examined randomized controlled trials, DEX administration decreased pain intensity. Zhao et al²⁹ used DEX for labor analgesia and showed that a low concentration of epidural ropivacaine (0.125%) combined with DEX (0.5 μg/kg) could reduce the feeling of pain. The results of our study

Table 5 Adverse Reactions and Neonatal Outcomes

Variable	Dexmedetomidine Group (n =72)	Standard Care Group (n =73)	P-value
Adverse reactions, no. (%)			
Bradycardia	5 (6.9)	2 (2.7)	0.275
Nausea	8 (11.1)	21 (28.8)	0.012 [#]
Vomiting	4 (5.6)	10 (13.7)	0.158
Hypersomnia	3 (4.2)	0 (0)	0.366
Hypertension after delivery, no. (%)	4 (5.6)	2 (2.7)	0.681
Hypotension after delivery, no. (%)	8 (11.1)	6 (8.2)	0.556
Exhaust time (hr), mean (SD)	34.53 (9.52)	38.13 (11.71)	0.044 [#]
NABA, median (IQR)			
1st day after delivery	38 (3)	37 (2)	0.173
2nd day after delivery	38.5 (2)	38 (2)	0.312

Notes: Data are presented as mean (SD), median (IQR), or number (%).

[#]Significant differences are at P<0.05.

Abbreviations: SD, standard deviation; IQR, interquartile range; NBNA, neonatal behavioral neurological assessment.

showed that the maternal rest and movement VAS scores of the DEX group were better than those of the standard care group in the overall comparison of multiple time points. However, for only resting pain at 6 and 12 hrs and movement pain at 12 hrs after delivery, the VAS score of the DEX group was lower than that of the standard care group. This is probably because we used the Bonferroni correction to set a relatively strict significant difference boundary value in the comparison of each time point, while the pain relief in the DEX group may actually have been more significant than that in the standard care group. Collectively, taking the results of this investigation together with those of previous studies, one can state with greater confidence that the inclusion of DEX was the reason for the analgesic effect.

The dose and intervention of DEX we chose was similar to those used in previous research.^{16,30} Dexmedetomidine can be safely used in adults, and the dose used in this study is completely acceptable.³¹ There was no significant difference between the DEX group and the standard care group in drug-related adverse events (such as severe bradycardia or fluctuation in blood pressure), which is in agreement with other reports.^{32,33} Moreover, Ao et al³³ reported that DEX can efficiently attenuate the maternal cardiovascular response during cesarean section. Nevertheless, based on the number of occurrences, bradycardia and hypersomnia in the DEX group

were indeed higher than those in the standard care group, which deserves attention. Yoshimura et al³⁴ used DEX in women undergoing elective cesarean section under spinal anesthesia and found that the DEX milk-to-plasma ratio did not exceed 1 in any participant, and the relative infant dose was very low; maternal sedation using DEX is unlikely to be harmful for the infant. Similarly, there was no difference in NBNA scores within two days postpartum in this study, indicating that DEX had no effect on infants. In short, DEX is safe in the context of cesarean section.

Intraoperative infusion of dexmedetomidine can put the mother to sleep, which may lead to the unblinding of the anesthesiologist in this study. In this regard, we considered this factor in our research protocol, so the attending physician responsible for anesthesia during this study was not involved in the study design, postoperative follow-up, or statistical analysis; that is, this study did not blind the intervention implementers. Subjects, study designers, follow-up staff, and statistical analysts were strictly blinded throughout the study. In addition, another point to explain is that we required the mothers to expect exclusive breastfeeding for more than 3 months as a component of the inclusion criteria for this trial. This is based on the consideration that there may indeed be some parturients who are willing to breastfeed exclusively before surgery and refuse breastfeeding after surgery. Setting this particular inclusion criterion can help reduce some potential causes of breastfeeding disruption, such as the termination of maternity leave and work. This ultimately reduced bias due to fluctuations in breastfeeding willingness.

Several limitations of this study warrant consideration. First, we did not set different dose groups to determine the optimal dose of DEX for breastfeeding. However, to our knowledge, this study is an early attempt to explore the effects of dexmedetomidine on breastfeeding, and our main objective was to determine the association between dexmedetomidine and breastfeeding. Second, there are many influential factors of breastfeeding after delivery, and we were unable to follow up all of them. However, we used survival analysis to capture early breastfeeding differences between the two groups as much as possible, and strict randomization and allocation concealment also helped to balance these factors between groups. Therefore, we believe that the results of this study are still reliable. Third, we did not perform intention-to-treat analysis in this study. Based on the flowchart of this study, it can be seen that during the follow-up process, a small number of parturients were excluded because the neonates were

admitted to the NICU. However, breastfeeding data were completely lost for these parturients after delivery. Even if we wanted to perform intention-to-treat analysis, complete full analysis set data were not available, so per-protocol analysis was still adopted.

Currently, anesthesiologists have done limited work to improve breastfeeding, and our research shows that applying DEX during the perioperative period of cesarean section can improve early breastfeeding outcomes, which gives us a better drug option for obstetric anesthesia. In the future, we can further explore new drugs or methods that may be beneficial for breastfeeding during cesarean section and labor analgesia. Of course, the results of the present study still need to be confirmed by prospective randomized controlled studies with larger sample sizes.

Conclusion

We concluded that intravenous application of DEX in the perioperative period of cesarean section was not only conducive to the early conversion of neonatal feeding to exclusive breastfeeding but could also improve the recovery quality and comfort of the parturient, optimize analgesia, shorten the time to first lactation, and increase lactation. Additionally, there were no significant adverse effects.

Data Sharing Statement

Six months after the main results are published, the individual participant data of this research report can be accessed with the permission of the corresponding authors. The study protocol, statistical analysis plan, and clinical study report will also be available.

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Disclosure

The authors report no conflicts of interest in this work.

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