# Effect of dexmedetomidine combined with ropivacaine transversus abdominal block (TAP) on opioid dosage after cesarean section under multimodal analgesia

Study period: November 01, 2022 - October 31, 2023

Version number: V2.0

Release date: November 28, 2022

## Background

Pain after cesarean section has always been one of the key points and difficulties in perioperative management. The ideal analgesia after cesarean section should aim at early mobilization of the parturient, reducing maternal and infant adverse reactions, accelerating functional recovery [1] . Due to the opening of the second-child and third-child policies, the proportion of cesarean sections has increased year by year, and the cesarean section rate in my country has risen from 28.8% in 2008 to 36.7% in 2018 [2]. Women who undergo cesarean section often experience moderate to severe pain. Studies have shown [3-4]: the incidence of moderate to severe pain within 24 hours after cesarean section ranges from 40% to 90%. Our previous retrospective studies also suggested that the incidence rate of moderate to severe pain after cesarean section in our hospital from 2017 to 2020 is 88.64% [5]. Incomplete postoperative analgesia may lead to overuse of opioids, delay recovery of maternal function, impact on mother-infant contact, and may even develop into chronic pain, and increase the risk of postpartum depression[6]. The European Society for Regional Anesthesia and Pain Management (ERSA) and the Association of Obstetric Anesthesiologists (OAA) recommend multimodal analgesia for pain management in cesarean section [7]. The American College of Obstetricians and Gynecologists also advocates providing multimodal optimized analgesia to improve postpartum pain, so as to reduce the dual impact of pain on the mother's psychology and physiology. Among them, the implementation of TAP block at the end of the operation and the regular oral administration of NSAIDS after the operation are also one of the important components of multimodal analgesia in the perioperative period of cesarean section.

Ultrasound-guided TAP is mainly used for lower abdominal surgery by blocking the lateral cutaneous branch and anterior cutaneous branch of the T6-L1 segment in the transverse abdominis plane [8]. Studies have pointed out that TAP block is more advantageous for postoperative analgesia in puerpera who have not received intraspinal morphine injection [9]; some studies have also shown that: although the sheath The postoperative analgesic effect of endomorphine was better than that of the TAP group, but the postoperative activity recovery time and postoperative ambulation time of the TAP group were shorter, and the recovery of gastrointestinal function was earlier. Compared with intrathecal morphine, TAP block is more beneficial to expedite post-cesarean recovery.

At present, the most commonly used local anesthetic for TAP blockade is ropivacaine, because

ropivacaine has the characteristics of low cardiotoxicity and good sensorimotor block separation, but its short duration of action limits its clinical application. Dexmedetomidine, on the other hand, is a highly selective α2-receptor agonist widely used as an adjuvant to local anesthetics in regional block [11]. When dexmedetomidine is used in combination with local anesthetics, it can enhance analgesic efficacy and prolong the duration of analgesia and reduce the consumption for postoperative opioid analgesics [11,12].

There are few reports on the effect of ultrasound-guided TAP block with dexmedetomidine combined with ropivacaine in multimodal analgesia after cesarean section. Moreover, few studies have mainly studied the prolongation of the analgesic effect time of dexmedetomidine, and the impact on postoperative opioid consumption has not been involved [12-15].

Hydromorphone is a derivative of morphine. It is a semi-synthetic powerful opioid analgesic drug. It mainly acts on opioid receptors (μ, δ). The analgesic effect is 5 to 10 times that of morphine. It is highly fat-soluble and has It has the advantages of quick onset, strong analgesic effect, inactive and non-toxic metabolites, and less adverse reactions. Studies have shown that hydromorphone has a significant effect in the treatment of acute pain in viscera. Hydromorphone intravenous patient-controlled analgesia can be effectively used for cesarean section Postoperative analgesia has been widely used abroad for acute severe pain and postoperative patient-controlled analgesia [16,17]. Postoperative intravenous analgesia is the routine analgesic program after cesarean section in my country, and within 2 days after cesarean section, maternal milk secretion is generally small (average <10 ml/d), and gradually increases after 2 days. It was found that [18] short-term use of clinically routine doses of morphine after delivery, the drug concentration in colostrum is extremely low, and the intake of newborns is negligible, while the fat solubility of hydromorphone is between morphine and fentanyl Between the series of drugs, the amount of milk secretion is small. Therefore, intravenous analgesia for only 48 hours after surgery is also safe from the perspective of breastfeeding. Our previous retrospective study [5] showed that the continuous use of opioids in routine PCIA of cesarean section women can cause dizziness, hypotension, nausea and vomiting, bradycardia, less time to get out of bed and other opioid adverse reactions. May affect a mother's ability to effectively care for her newborn. In this study, the use of background-free PCIA in the context of multimodal analgesia can greatly reduce the amount of postoperative opioids used, reduce the incidence of postoperative adverse reactions, and

it is easier to meet the requirements of obstetrics to reduce postoperative pain while improving postoperative pain. Analgesic needs for opioid use.

Based on this, the main hypothesis of this study is that dexmedetomidine combined with ropivacaine TAP block under multimodal analgesia can reduce the consumption of opioids after cesarean section compared with ropivacaine TAP alone. This study aims to evaluate the efficacy of dexmedetomidine as an adjuvant of ropivacaine in TAP block in cesarean section women under multimodal analgesia, and to explore the suitable multimodal analgesia method for cesarean section, so as to better Good guidance for cesarean section perioperative analgesic management.

## Research Purpose

1. The main purpose: To evaluate the efficacy of dexmedetomidine as an adjuvant of ropivacaine in TAP block in women undergoing cesarean section under multimodal analgesia

2. Secondary purpose: To optimize the multimodal analgesic scheme for cesarean section and guide perioperative analgesic management

## Research design

Single-center, randomized, double-blind, parallel controlled clinical trials.

### 1.1 Randomization

In this study, the method of block random grouping was used for random grouping, and the block size was set to 4 and 6. The random results were generated by researcher A using R or Excel software, and the randomized results were sealed in envelopes and handed over to The anesthetized nurse opened the envelope for randomization after confirming that the puerpera was enrolled before the end of the operation.

### 1.2 Blinding

After the TAP blocker was prepared by the anesthetist nurse and blocked, the anesthesiologist who performed the TAP block, the postoperative follow-up personnel, the researchers who collected data and the puerpera were blinded.

### 1.3 Sample size

The primary outcome measure was hydromorphone consumption 48 hours after surgery. Referring to the data in previous similar studies[8], the consumption of hydromorphone at 48 hours after operation was normally distributed, and the sample size can be calculated by using the difference test, and the consumption of opioids at 48 hours after operation in the control group ( Expressed in morphine

equivalent), the mean value is 20.8mg, the standard deviation is 4.18, and the intervention group is expected to reduce by 15%[19], it is calculated by PASS 2015 software that at least 80 patients need to carry out the difference test to have 90% power to identify significant differences at the level of α = 0.05 (two-sided test). Considering the dropout rate of 10%, at least 90 patients, 45 in each group, should be included in this study.

### 1.4 Indications

PCIA is widely used for postoperative analgesia of cesarean section women because of its easy operation and management. As a semi-synthetic powerful opioid analgesic drug, hydromorphone hydrochloride has the characteristics of fast onset of action, strong analgesic effect, inactive and non-toxic metabolites, and few adverse reactions. It has been widely used in acute severe pain abroad, and postoperative patient-controlled analgesia. Many guidelines now regard TAP block as one of the important components of multimodal analgesia after cesarean section for analgesia after cesarean section.

## Research steps

### 2.1 Selected

Parturients must meet all the inclusion criteria and exclusion criteria before they are eligible to participate in the study. After determining the eligibility of the parturients, the researchers fully explain the nature, purpose and risks of the test to the subjects before the test, teach the use of PCIA, and use Patients are convinced that they have the right to withdraw at any time after agreeing to participate, and the subjects should sign written informed consent after fully considering and agreeing to participate in the trial. The case report form used in this study should properly document the process of obtaining informed consent.

Researcher A handed the grouping envelope to the anesthesia nurse before the operation, and the subjects will be randomly assigned to one of the following two groups according to the ratio of 1:1: the experimental group is dextromethanone 0.5ug/kg+0.25% ropivacaine 20mlTAP Block, the control group was 0.25% ropivacaine 20mlTAP block on each side. The PCIA analgesic regimen of the two groups was the same, hydromorphone hydrochloride injection 10mg, diluted to 100ml with 0.9% sodium chloride injection, the analgesic pump parameters were no background dose, single dose 2.0ml/time, and the lock-in time was 10min.

**2.2 Preoperative and intraoperative anesthesia management**

1) After the puerpera was admitted to the hospital, all inspections were completed, food was fasted for 6 hours, drinking was forbidden for 2 hours, and there was no preoperative medication. After entering the operating room, the upper limb venous channel was opened, blood pressure, heart rate, electrocardiogram and pulse oxygen saturation were routinely monitored, and oxygen inhalation by face mask was 3-5L/min.

2) Anesthesia method: All anesthesia is performed by an experienced anesthesiologist. Ask the parturient to perform puncture in the right lateral position. The puncture gap is L2-3/L3-4. After the resistance disappearance method is used to confirm the epidural space, a 5G pen-tip spinal anesthesia needle is inserted. After clear cerebrospinal fluid is seen, 0.66% Bubi Caine 10mg (0.75% bupivacaine 1.4-1.6ml + 50% glucose injection 0.2-0.3ml), indwelling epidural catheter. After the parturient lies on her back, the left side is raised by 15[. ]. After confirming that the level of anesthesia reaches T6, disinfect and spread the drape to start the operation.

3) Intraoperative management and multimodal analgesia: Dexamethasone 10 mg and parecoxibna 40 mg were given after the fetus was delivered and the umbilical cord was cut off.

4) After the operation, transversus abdominis plane block (TAP) was performed in the PACU according to the surgical site and grouped according to the envelope, and the operating anesthesiologist was not aware of the grouping situation. TAP is performed by a senior physician in the PACU under the guidance of ultrasound. The parturient takes a half-lying position, and places the ultrasound probe perpendicular to the skin at the level of the midaxillary line. After confirming the structure of each layer of the abdomen, gradually move the probe toward the lumbar spine. When the quadratus lumborum muscle at the edge of the spine is seen, insert the puncture needle parallel to the probe (in the plane), so that the needle tip is located at the junction of the posterior side of the transversus abdominis muscle and the front side of the quadratus lumborum muscle, and separate the two layers of muscle with normal saline to determine Inject after the needle tip. The ultrasound image shows that the liquid medicine has diffused and infiltrated, and the ultrasound image is collected. In the later stage, another senior physician judges the quality of TAP based on the ultrasound image.

5) Prevention of nausea and vomiting: Palonosetron 0.25 mg was given after the fetus was

delivered and the umbilical cord was cut off.

**2.3 postoperative**

The puerpera was sent back to the maternity ward, and the analgesic pump was turned on in the ward and the start time was recorded. Postoperative oxygen inhalation and monitoring time were routinely handled in the ward. After 48h. The patient performed PCA by pressing the analgesic pump. If the analgesic effect was still unsatisfactory or the postoperative follow-up maternal resting NRS>3 points or active NRS>6 points, hydromorphone 0.3-0.5 mg was given for rescue analgesia. Follow-up at 4h, 24h, and 48h after operation recorded maternal hydromorphone consumption, resting and active NRS scores, uterine contraction pain scores, blood pressure, heart rate, respiratory rate and other vital signs, and whether there were adverse reactions to opioids. Postoperative nausea and vomiting of the puerpera was followed by routine use of antiemetics and records were made. PCIA was stopped when necessary and the time and consumption were recorded.

**2.4 Possible adverse reactions and treatment measures during the study**

Although the TAP block is performed under ultrasound guidance, and the local anesthetic is withdrawn before injection to confirm that the drug is not pushed into the blood vessel, local anesthetic poisoning may still occur, and oxygen inhalation or even assisted ventilation may occur if necessary. The following situations may occur in conventional PCIA treatment: the opioid hydromorphone in PCIA treatment may cause nausea, vomiting, fatigue and itching, etc., and antiemesis and drug withdrawal may be performed if necessary; when severe respiratory depression occurs, stop Drugs, oxygen inhalation, naloxone to antagonize opioids, and even assisted ventilation.

**case selection**

**1. Inclusion criteria**

1） 37-42 weeks of gestation

2） Plan cesarean section

3） Postoperative PCIA analgesia

4） Age > 18 years old

5） ASA I-III grade

6） Participate in the trial voluntarily and obtain informed consent

**2.Exclusion criteria**

1） Cesarean section with general anesthesia or neuraxial anesthesia with epidural administration

2） Combination of other epidural drugs during operation

3） High-risk pregnancy (multiple pregnancy, in vitro fertilization, etc.) or pregnancy-related complications (hypertension, preeclampsia, chorioamnionitis, etc.)

4） The number of cesarean sections in the past ≥ 3

5） BMI≥50kg/$m^2$ is not suitable for TAP block

6） Hypersensitivity or contraindications to the drugs involved in the study

7） Combined with surgery other than tubal ligation and oophorectomy

8） Severe renal impairment (SCr>176μmol/L and/or BUN>17.9 mmol/L]), severe live r impairment (ALT and/or AST more than 3 times the upper limit of normal value)

9） Coagulation dysfunction or increased bleeding risk (PLT<80×109/L or INR>1.5)

10） History of chronic pain or opioid abuse

11） Enrolled in other clinical trials in the past three months

**3. Elimination criteria**

1） Other treatment measures are required due to complications or changes in the condition, and it is not suitable to continue to accept the study;

2） Emergency blinding measures were taken during the study;

3） The subject requested to withdraw from the study.

**4. Termination criteria**

1） There are important policy and regulatory risks in the research that lead to the termination of the research;

2） An unexpected risk situation that is unacceptable to the subject occurs during the research;

3） The decision to terminate the study was made by an expert committee and all parties involved in the study were notified of the reasons for the termination.

## Research methods and technical routes

**1. The name and specification of the drug used in the study**

1) Study drug:

① Dexmedetomidine

[Manufacturer] Jiangsu Hengrui Pharmaceutical Co Ltd.

[Approval Number] Guoyao Zhunzi H20130093

[Ingredients] dexmedetomidine hydrochloride, excipients: sodium chloride

[Properties] Colorless or almost colorless clear liquid

[Indications] Sedation during tracheal intubation and mechanical ventilation in surgical patients under general anesthesia

[Specification] 2ml: 200ug

[Storage] Shade, airtight, store at room temperature

[Packing] vial packaging, 5 bottles/box, 10 bottles/box

[Validity] 18 months

② Ropivacaine

[Manufacturer] AstraZeneca AB

[Approval number] Import drug registration certificate number H20140763

[Ingredients] Ropivacaine hydrochloride, excipients: sodium chloride, hydrochloric acid/sodium hydroxide and water for injection.

[Properties] Colorless clear liquid.

[Indications] Suitable for surgical anesthesia and acute pain control

[Specification] 10ml: 100mg

[Storage] Store at room temperature below 30℃, avoid freezing

[Packing] Packed in plastic ampoules, 5 pieces/box.

[Validity] 36 months.

③ Hydromorphone

[Manufacturer] Yichang Renfu Pharmaceutical Co Ltd.

[Approval Number] Guoyao Zhunzi H20120100

[Ingredients] hydromorphone hydrochloride, excipients: citric acid, sodium citrate, water for injection.

[Properties] Colorless clear liquid.

[Indications] It is suitable for patients who need to use opioids for analgesia.

[Specification] 2ml:2mg

[Storage] Shade, keep in airtight storage.

[Packing] Low borosilicate glass ampoules, 10 pieces/box.

[Validity Period] 24 months.

2) Drug solvent: 0.9% sodium chloride injection, use the product in 100ml package.

3) Test equipment: Fornia electronic micropump

[device name]: Disposable electronic micropump

[Approval number]: State Food and Drug Administration (quasi) word 2009 No. 3540501 (more)

[Specification]: CPE-101, CPE-201

[Indications]: Used for continuous micro-injection of analgesic drugs and other drugs for patients

[Manufacturer] : Zhuhai Fornia Medical Equipment Co., Ltd.

**2. Treatment**

The research factor of this study is the medication of TAP blockade. The subjects will be randomly assigned to two groups according to the ratio of 1:1. block. The analgesic drug regimens of the two groups were the same, both were hydromorphone hydrochloride injection 10mg, diluted to 100ml with 0.9% sodium chloride injection, the parameters of the analgesic pump were set the same, both had no background dose, and the single dose was 2.0ml/time , the locking time is 10 minutes. The grouping envelope is handed over to the anesthesia nurse after the patient enters the operating room to confirm the grouping. At the end of the operation, the latter prepares the blocking drug according to the grouping situation and hands it to the experienced anesthesiologist to perform TAP block. After the patient returns to the ward, the analgesic pump is turned on. .

**3. Combined medication**

During the puerpera’s operation, parecoxibna, dexamethasone, and palonosetron can be combined for multimodal analgesia. In addition to PCIA drugs and salvage analgesia plus hydromorphone hydrochloride after the operation, acetaminophen oral solution can also be taken orally. and celecoxib capsules for pain relief.

**4. Drug management**

This product is a commonly used drug for analgesia in the anesthesiology department.

## Observation items and detection timing

**1. Subject screening period**

1) Collect demographic data: height (cm), weight (kg), age (yr), gestational age, ASA classification, parity, and ask whether the mother has any history of complications during pregnancy or chronic diseases (combined diseases during pregnancy, liver and kidney) heart disease, hypertension, diabetes, chronic pain, pain management, history of alcohol and opioid use);

2) Collect preoperative clinical data: systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and other vital signs, available preoperative laboratory tests (blood routine, blood biochemistry, coagulation function, electrocardiogram, etc.);

**2. Surgical treatment period**

3) At the end of the operation, the anesthesia method, puncture gap, operation name, operation duration, anesthesia duration, intraoperative combined medication, intake and output volume, etc. are obtained through the surgical anesthesia information system

**3. PCIA treatment period**

4) Hydromorphone consumption at 4h, 24h, 48h after operation and press PCA times at 4h, 12h, 24h, 48h after surgery

5) Press PCA time for the first time

6) the rest and activity NRS score and the uterine contraction pain NSR score at 4h, 24h, and 48h after surgery, were visited respectively;

7) Postoperative Ramsay score 4h, 24h, 48h postoperatively and presence or absence of opioid adverse reactions

8) The first time to get out of bed after the puerpera

**4. End of PCIA**

9) The incidence of rescue analgesia 48 hours after operation, and the satisfaction degree of postoperative analgesia of self-designed parturients;

10) Obtain the length of postoperative hospital stay through the electronic medical record system

**Efficacy evaluation standard**

**1. Main outcome indicators:**

The main outcome measure was hydromorphone consumption (mg) 48 hours after surgery

**2. Secondary outcome indicators:**

1) Hydromorphone consumption at 4h and 24h after operation, first PCA time, PCA times at 4h, 6h, 12h, 24h, and 48h after operation, NRS resting, activity score, and contraction pain score at 4h, 24h, and 48h after operation NRS score: digital pain assessment scale, with 11 numbers from 0-10 instead

of the words indicate the degree of pain, 0 means no pain, 10 means the most pain.

Rest score: quiet, resting state; Activity score: when turning over at 90°

Contraction Pain Score: Maximum pain score for uterine contractions induced by breastfeeding or administration of oxytocin during the specified time interval.

3) Ramsay Sedation Score

4) Satisfaction rate of postoperative pain relief in self-designed parturients

**3. Other outcome indicators:**

The incidence of postoperative adverse reactions and rescue analgesia

① Hypotension: systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg or <20% of baseline

② Respiratory depression: Respiratory rate < 10 breaths/min or SpO2 < 90%

③ Bradycardia: heart rate <60 beats/min

④ Dizziness, nausea and vomiting, skin itching, etc.

**Statistical processing**

**1. Analyze the crowd**

1) Full analysis set (FAS): subject set according to the principle of Intention To Treat (ITT): refers to the data set composed of all subjects participating in the treatment and having baseline efficacy evaluation.

2) Per-protocol set (PPS): Refers to the completed trial and excluded the treatment population group that seriously violated the protocol (meaning that the research subjects violated the inclusion criteria or exclusion criteria).

3) The curative effect analysis will be carried out on the basis of the full analysis set and the protocol set. All analyzes of baseline demographic data will be performed on the basis of the full analysis set.

**2. Statistical analysis methods**

First, descriptive statistical analysis was used to compare the baseline data (age, gestational week, BMI, operation time, etc.) of the subjects between random groups. The KS test was used to test the normality of the measurement data. The normal distribution measurement data was expressed as mean ±standard deviation ($\bar{x} \pm s$), the skewed distribution measurement data was expressed as the median (P25, P75), and the count data was expressed as frequency ( Composition ratio) for statistical description.

All of the following statistical analyzes were performed using SPSS 26.0 statistical software, and all hypothesis tests were performed with two-sided tests. Exploratory results are reported descriptively only.

2.1 Main outcome indicators:

The main outcome indicators were hydromorphone consumption 48 hours after operation, using two-sample independent t-test. Hypothesis testing was performed as a two-sided test, and $P<0.05$ was considered statistically significant. For the main outcome indicators, two-sample independent t-test or Mann-Whitney u-test were used for comparison according to their normality; subgroup analysis could be performed according to age, BMI, operation time, ASA grade, education level, and quality of TAP block.

2.2 Secondary outcome indicators:

The consumption of hydromorphone at 4h and 24h after operation, the number of PCA at 4h, 6h, 12h, 24h, and 48h after operation, and the time of the first PCA were analyzed by two-sample independent t-test, $P<0.05$ was statistically significant

Two-sample Wilcoxon rank sum test was used to compare the postoperative Ramsay score and self-designed maternal analgesia satisfaction

Chi-square test or Fisher's exact test were used to compare the incidence of postoperative opioid adverse reactions and rescue analgesia

Repeated measures analysis of variance was used to compare the NRS scores at 6h, 24h, and 48h after operation between the groups

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