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ORIGINAL ARTICLE

# Effects of ropivacaine alone or in combination with dexmedetomidine on cesarean section: a systematic review and meta-analysis

## *Efectos de la ropivacaína sola o en combinación con dexmedetomidina en la cesárea: revisión sistemática y metaanálisis*

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## Abstract

**Objective:** *Different from physiological pain, post-operative pain is caused by surgical trauma. We aimed to systematically assess the effects of ropivacaine alone or in combination with dexmedetomidine on cesarean section and to conduct a meta-analysis.* **Methods:** *According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and Cochrane intervention system review manual, retrieval software and data analysis tools were used for literature retrieval, screening, exclusion and inclusion, data extraction, analysis and statistics, and risk assessment. A total of 37 literatures were retrieved, and 11 literatures were left after 26 duplicates were excluded.* **Results:** *A total of 37 literatures were retrieved in all databases, of which 11 literatures were left and finally 7 all published in English were obtained. They were seven randomized controlled trials on ropivacaine alone or in combination with dexmedetomidine applied in 502 parturients receiving cesarean section. The results of meta-analysis on main outcome indices showed that the number of parturients in need of rescue ($\chi^2$ = 28.62, p < 0.001, $I^2$ = 93%), incidence rate of adverse reactions ($\chi^2$ = 28.66, p = 0.007, $I^2$ = 55%), satisfaction ($\chi^2$ = 7.97, p = 0.05, $I^2$ = 62.3%), visceral respiratory response ($\chi^2$ = 19.26, p < 0.001, $I^2$ = 89.6%), satisfaction with muscle relaxation ($\chi^2$ = 6.92, p = 0.03, $I^2$ = 71.1%), and spinal anesthesia grade ($\chi^2$ = 25.89, p < 0.01, $I^2$ = 92.3%).* **Conclusions:** *Ropivacaine combined with dexmedetomidine has a better prognostic effect on cesarean section and causes fewer adverse reactions.*

***Keywords:*** *Ropivacaine. Dexmedetomidine. Cesarean section. Meta-analysis.*

## Resumen

**Objetivo:** *A diferencia del dolor fisiológico, el dolor posoperatorio está ocasionado por un trauma quirúrgico. El objetivo es evaluar sistemáticamente los efectos de la ropivacaína sola o en combinación con dexmedetomidina en la cesárea y realizar un metaanálisis.* **Métodos:** *De acuerdo con la declaración PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement) y el Cochrane Intervention System Review Manual, se utilizaron software y herramientas de análisis de datos para la recuperación de la literatura, los exámenes de detección, la exclusión y la inclusión, la extracción de datos, el análisis y las estadísticas, y la evaluación del riesgo. Se obtuvieron 37 estudios, de los cuales quedaron 11 después de excluir 26 duplicados* **Resultados:** *De las bases de datos se obtuvieron 37 estudios, de los cuales se seleccionaron 11 y finalmente se obtuvieron 7, todos publicados en inglés. Correspondieron a 7 ensayos controlados aleatorizados sobre ropivacaína sola o en combinación con dexmedetomidina en 502 parturientas sometidas a cesárea. Los resultados del metaanálisis*

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*sobre los principales índices de resultados mostraron que el número de parturientas con necesidad de rescate ($\chi^2$ = 28.62; p < 0.001; $I^2$ = 93%), la tasa de incidencia de reacciones adversas ($\chi^2$ = 28.66; p = 0.007; $I^2$ = 55%), la satisfacción ($\chi^2$ = 7.97; p = 0.05; $I^2$ = 62.3%), la respuesta respiratoria visceral ($\chi^2$ = 19.26; p < 0.001; $I^2$ = 89.6%), la satisfacción con la relajación muscular ($\chi^2$ = 6.92; p = 0.03; $I^2$ = 71.1%), el grado de anestesia espinal ($\chi^2$ = 25.89,; p < 0.01; $I^2$ = 92.3%).* **Conclusiones:** *La ropivacaína combinada con dexmedetomidina tiene un mejor efecto pronóstico en la cesárea y provoca menos reacciones adversas.*

***Palabras clave:*** *Ropivacaína. Dexmedetomidina. Cesárea. Metaanálisis.*

# Introduction

Different from physiological pain, post-operative pain is caused by surgical trauma. After tissue injury at the surgical incision, inflammatory mediators are released under stress, and then the sensory nerves feel the conduction of stimulus of inflammatory mediators to the center. The pain sensitivity of patients also changes postoperatively, thereby producing an unpleasant emotional expression in the cerebral cortex, which is the protective response of the body to harmful stimuli[1]. Post-operative pain is one of the most common problems faced by patients, which is not conducive to the rapid post-operative recovery of patients, and the severer the pain is, the greater the patient's physiological and psychological fluctuation will be[2]. In general, the pain is the severest within 2 days after surgery, and it mostly lasts for < 1 week. If not controlled well, post-operative pain may transform into chronic pain or persistent pain, and even neuropathic pain in severe cases.

With the opening of the two-child policy in China, the cesarean section rate has been increasing. After cesarean section, incision pain and uterine contraction pain are serious problems faced by parturients[3]. Postpartum pain is an important factor causing anxiety, depression and insomnia in parturients, seriously affecting the post-operative rehabilitation and lactation, and also affecting parturients' care for newborns. Therefore, multi-modal analgesia is adopted after cesarean section. Post-operative analgesia methods commonly used in clinic include patient-controlled epidural analgesia (PCEA), patient-controlled intravenous analgesia (PCIA), oral administration or intramuscular injection and even intravenous infusion of opioids or antipyretic analgesics, and ultrasound-guided plane block of transverse abdominal muscle (TAP) popular in recent years[4,5]. Nowadays when minimally-invasive surgery is strongly advocated, cesarean section is considered as a cruel operation, after which parturients often suffer from highly severe pain. At present, PCEA and PCIA are mainly adopted by anesthesiologists for post-operative analgesia. However, these two analgesia methods lead to serious complications such as nausea and vomiting, pruritus, respiratory depression, epidural hematoma, hemodynamic instability, and even unsatisfactory analgesia[6]. Besides, systemic administration has limitations of drugs and short duration of action, causes severe gastrointestinal discomfort, nausea, vomiting, increased urinary retention, hepatic and renal dysfunction, and increased frequency of administration, and affects the rest and sleep quality of parturients.

At present, the local anesthetics used in TAP include lidocaine, bupivacaine, and ropivacaine. Among them, ropivacaine characterized by long duration of action, low toxicity, and good sensorimotor block separation has become a preferred local anesthetic in field block for anesthesiologists[7]. Despite a good analgesic effect in clinic, ropivacaine has short duration of block and fails to meet the demand for post-operative analgesia with one-time administration[8]. Therefore, local anesthetics with longer duration of action are needed, or local anesthetic adjuvants need to be rationally used to prolong the duration of action of local anesthetics, without causing any unnecessary complications to increase the duration of sensory block. Dexmedetomidine, a research hotspot in the field of anesthesia and analgesia, is often applied. As a highly-selective $\alpha$-adrenergic receptor agonist, dexmedetomidine is characterized by sedation, anti-anxiety, analgesia, stabilization of hemodynamics, inhibition on sympathetic nerve activity, and mild respiratory depression[9]. At present, dexmedetomidine has been widely used in intensive care unit sedation, non-invasive endoscopic examination, pre-operative medication, adjuvant medication during anesthesia, and post-operative analgesia[10]. Dexmedetomidine has been combined with bupivacaine to markedly prolong the sensory and motor block duration and to improve intraoperative and post-operative analgesia for women undergoing

cesarean section, without any significant complications for the mothers or infants[11]. However, there are few reports on the combination of dexmedetomidine and ropivacaine for analgesia in cesarean section. The present study aims to observe the analgesic effect of dexmedetomidine combined with ropivacaine on cesarean section and related adverse reactions, so as to provide a new idea for multi-modal analgesia.

## Methods

### *Literature retrieval method*

The retrieval strategy was developed according to Cochrane international standards and the PRISMA flowchart, and the English databases included PubMed, Web of Science, and EMbase.

- English retrieval words
  Dexmedetomidine, ropivacaine, cesarean delivery or cesarean section, and randomized controlled trial.
- Retrieval time period
  The retrieval was restricted to human randomized controlled trials in the above databases from the establishment to April 30, 2021.

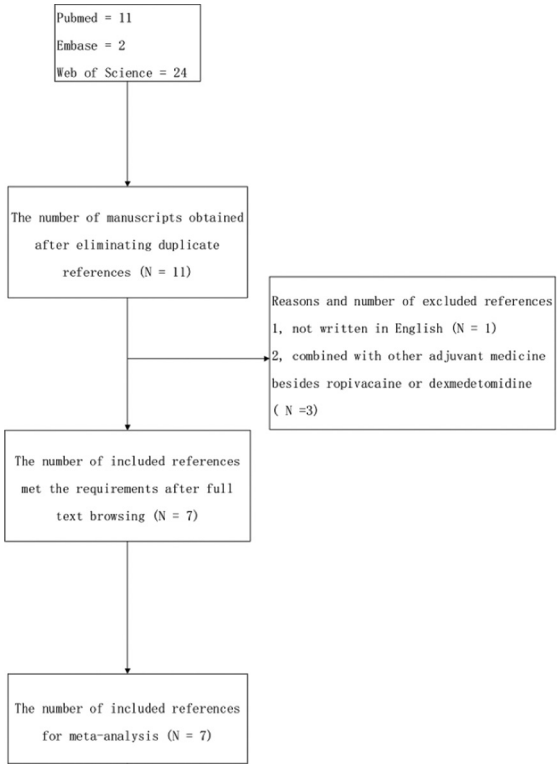


**Figure 1.** Preferred reporting Items for systematic reviews and meta-analysis flowchart.

### *Data extraction*

The basic information included the research title, first author, publication time, control group and observation group, intervention measures, and indices.

### *Literature quality assessment*

The quality of included literatures was assessed using the Cochrane risk of bias assessment tool, criteria for judging risk of bias in the risk of bias assessment tool, and possible approach for summary assessments of the risk of bias for each important outcome within and across studies designated by Cochrane.

### *Statistical analysis*

Meta-analysis was conducted for indices enrolled using RevMan5.4 provided by Cochrane, and the forest plot made by RevMan software was used to assess the publication bias.

Random effects model (REM) was used in the case of $I^2 > 50\%$ in heterogeneity test, while fixed effects model (FEM) was used in the case of $I^2 \leq 50\%$. The effect scale indices included two-category data and continuous data.

## Results

### *Literature retrieval results*

A total of 37 literatures were retrieved in all databases, and 11 literatures were left after 26 duplicates were excluded. Then, one literature was excluded according to the inclusion and exclusion criteria, and three literatures were excluded after reading the full text. Finally, seven literatures all published in English were obtained (Fig. 1).

### *Basic characteristics of included studies*

The indices, that is, the number of parturients in need of rescue, adverse reactions, satisfaction, incidence rate of transient neurological syndrome (TNS), visceral respiratory response, satisfaction with muscle relaxation, spinal anesthesia grade, mean time for rescue analgesia, visual analog scale (VAS) score, 24 h mean cumulative dose for rescue analgesia, pain-free

**Table 1. Basic characteristics of included studies**

| First author | Published year | Treatment/control group | Treatment method | Outcome index |
|---|---|---|---|---|
| Bi[12] | 2020 | 25/25 | Ropivacaine/ropivacaine + dexmedetomidine | 1, 5, 6, 7 |
| Qian[13] | 2020 | 35/35 | Ropivacaine/ropivacaine + dexmedetomidine | 1,9, 11, 12 |
| Bhardwaj[14] | 2017 | 30/30 | Ropivacaine/ropivacaine + dexmedetomidine | 1, 2, 3, 8, 9, 10 |
| Kong[15] | 2018 | 51/51 | Ropivacaine/ropivacaine + dexmedetomidine | 2, 4, 9, 13, 14 |
| Mo and Qiu[16] | 2017 | 40/40 | Ropivacaine/ropivacaine + dexmedetomidine | 2, 9, 13 |
| Tang[17] | 2020 | 30/30 | Ropivacaine/ropivacaine + dexmedetomidine | 2 |
| Zhao[18] | 2017 | 40/40 | Ropivacaine/ropivacaine + dexmedetomidine | 9 |

1: number of parturients in need of rescue; 2: adverse reactions; 3: satisfaction; 4: incidence rate of TNS; 5: visceral respiratory response; 6: satisfaction with muscle relaxation; 7: spinal anesthesia grade; 8: mean time for rescue analgesia; 9: VAS score; 10: 24 h mean cumulative dose for rescue analgesia; 11: pain-free duration; 12: time to first analgesia required; 13: Ramsay sedation score; 14: MMSE score.

duration, time to first analgesia required, Ramsay sedation score, and mini-mental state examination (MMSE) score, were covered in three studies, five studies, one study, one study, one study, one study, one study, one study, five studies, one study, one study, one study, two studies, and one study, respectively (Table 1).

## Quality assessment of included studies

The randomization method was known in all of the seven included studies. The allocation concealment was known in two studies and unknown in the remaining five studies. The blind method for subjects was unknown in three studies, and the blind method for result assessment was unknown in two studies. The outcome indices were incomplete in one study, and the selective reporting was high risk in one study and also unknown in one study (Fig. 2).

## Meta-analysis and publication bias

### Number of parturients in need of rescue

As shown in figure 3, the number of parturients in need of rescue was reported in three studies, the results belonged to two-category data, and REM was used ($I^2 > 50\%$). The results showed that the number of parturients in need of rescue in ropivacaine + dexmedetomidine group was significantly smaller than that in ropivacaine control group, and the difference was statistically significant ($\chi^2 = 28.62$, $p < 0.001$, $I^2 = 93\%$), indicating that ropivacaine combined with dexmedetomidine can significantly improve the prognosis of parturients receiving cesarean section.

### Incidence rate of adverse reactions

As shown in figure 4, the incidence rate of adverse reactions was reported in five studies, the results belonged to two-category data, and REM was used ($I^2 > 50\%$). The results showed that the incidence rate of adverse reactions in ropivacaine + dexmedetomidine group was significantly lower than that in ropivacaine control group, and the difference was statistically significant ($\chi^2 = 28.66$, $p = 0.007$, $I^2 = 55\%$), indicating that ropivacaine combined with dexmedetomidine can significantly reduce the incidence rate of clinical adverse reactions in parturients receiving cesarean section.

### Satisfaction of parturients

As shown in figure 5, the satisfaction of parturients was reported in one study, the results belonged to two-category data, and REM was used ($I^2 > 50\%$). The results showed that the number of parturients with excellent satisfaction in ropivacaine + dexmedetomidine group was significantly larger than that in ropivacaine control group, and the difference was statistically significant ($\chi^2 = 7.97$, $p = 0.05$, $I^2 = 62.3\%$), indicating that ropivacaine combined with dexmedetomidine can significantly enhance the satisfaction of parturients receiving cesarean section.

### Incidence rate of TNS

As exhibited in figure 6, the incidence rate of TNS was reported in 1 study, the results belonged to two-category data and FEM was used ($I^2 < 50\%$). The results revealed that the incidence rate of TNS in ropivacaine +

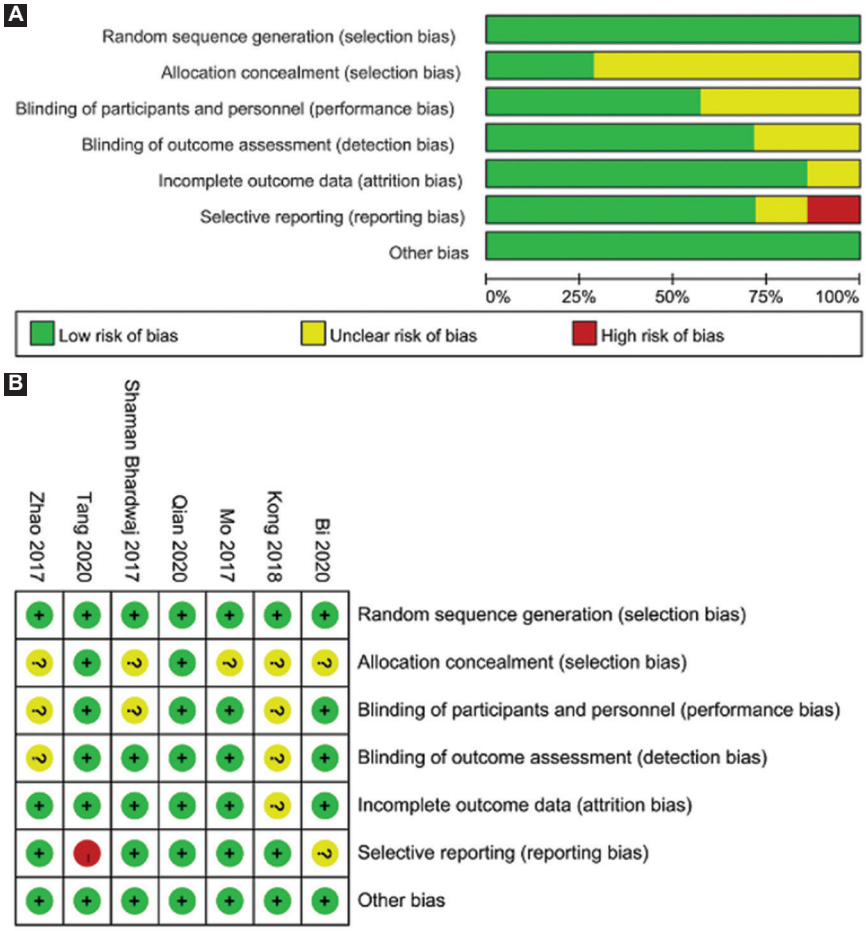


**Figure 2. A** and **B:** *Risk of bias of included literatures.*

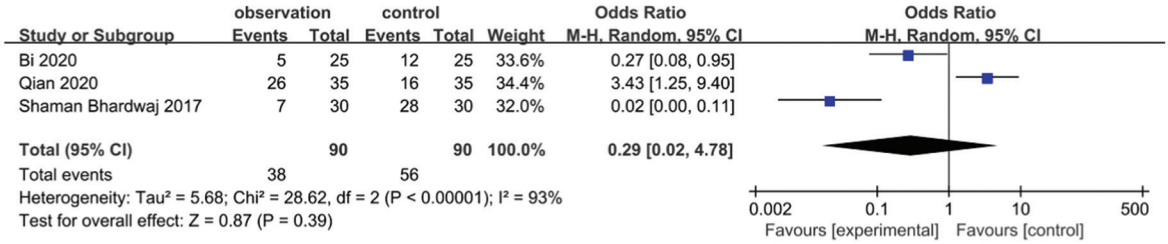


**Figure 3.** Forest plot of meta-analysis on the number of parturients in need of rescue in the two groups.

dexmedetomidine group was significantly lower than that in ropivacaine control group, and there was no statistically significant difference ($\chi^2$ = 0.16, p = 0.93, $I^2$ = 0%).

### *Visceral respiratory response*

As presented in supplementary data figure S1, the visceral respiratory response of parturients was reported in one study, the results belonged to two-category data, and REM was used ($I^2$ > 50%). The results revealed that the number of parturients with visceral respiratory response in grade 2 and 3 in ropivacaine + dexmedetomidine group was significantly smaller than that in ropivacaine control group, and there was a statistically significant difference ($\chi^2$ = 19.26, p < 0.001, $I^2$ = 89.6%), suggesting that ropivacaine combined with dexmedetomidine can improve the visceral respiratory response of parturients receiving cesarean section.

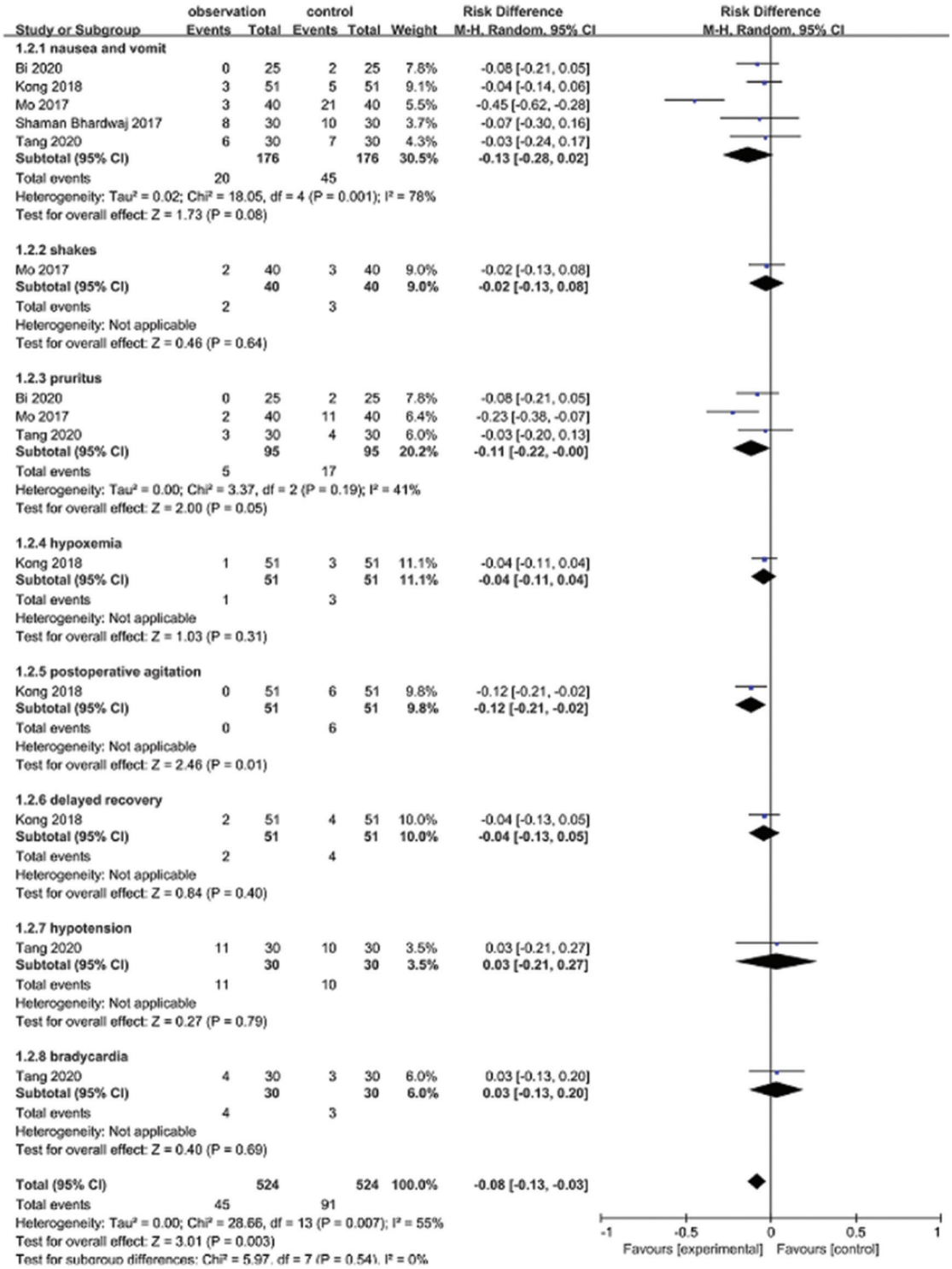


**Figure 4.** Forest plot of meta-analysis on the incidence rate of adverse reactions in the two groups.

### *Satisfaction with muscle relaxation*

As displayed in supplementary data figure S2, the satisfaction of parturients with muscle relaxation was reported in one study, the results belonged to two-category data and REM was used ($I^2 > 50\%$). The results revealed that the satisfaction of parturients with muscle relaxation in ropivacaine + dexmedetomidine

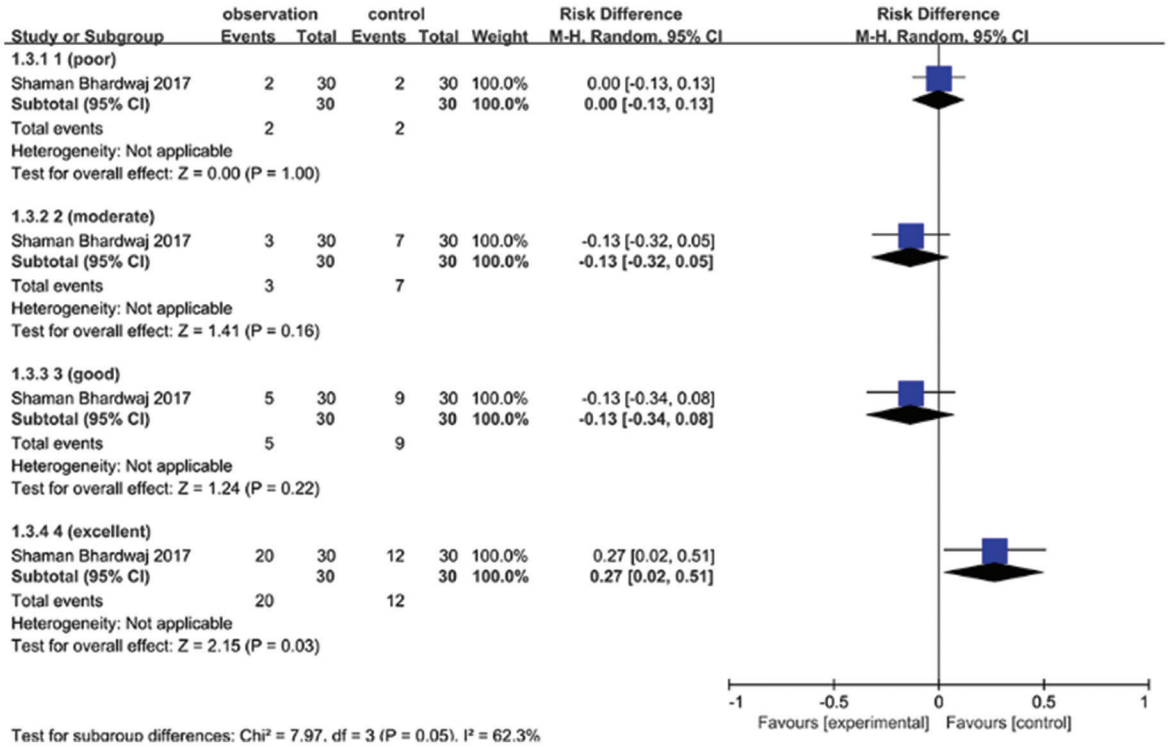


**Figure 5.** Forest plot of meta-analysis on the satisfaction of parturients in the two groups.

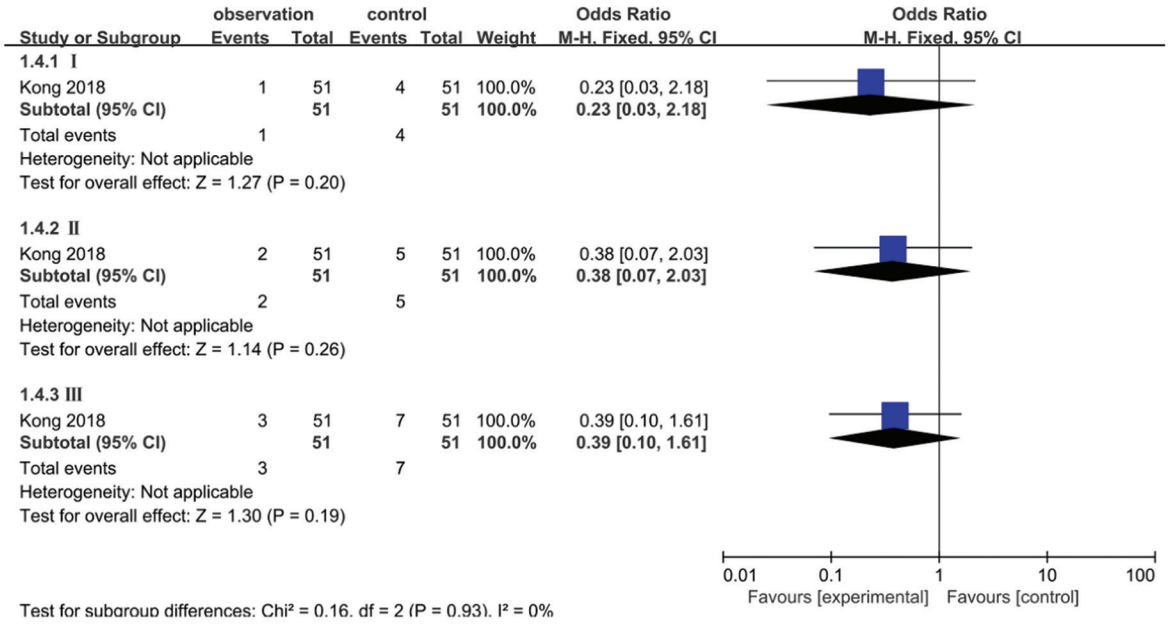


**Figure 6.** Forest plot of meta-analysis on the incidence rate of transient neurological syndrome in the two groups.

group was significantly higher than that in ropivacaine control group, and there was a statistically significant difference ($\chi^2$ = 6.92, p = 0.03, $I^2$ = 71.1%), suggesting that ropivacaine combined with dexmedetomidine can raise the satisfaction of parturients receiving cesarean section with muscle relaxation.

### Spinal anesthesia grade

The spinal anesthesia grade of parturients was reported in 1 study, the results belonged to two-category data and REM was used ($I^2$ > 50%) (Supplementary data Fig. S3). The results manifested that the number of parturients receiving spinal anesthesia in grade 2 and 3 in ropivacaine + dexmedetomidine group was significantly smaller than that in ropivacaine control group, and there was a statistically significant difference ($\chi^2$ = 25.89, p < 0.01, $I^2$ = 92.3%), suggesting that ropivacaine combined with dexmedetomidine can lower the spinal anesthesia grade of parturients receiving cesarean section.

### Mean time for rescue analgesia

The mean time for rescue analgesia of parturients was reported in one study, the results belonged to continuous data, and REM was used ($I^2$ > 50%) (Supplementary data Fig. S4). The results manifested that the mean time for the 4th and 5th rescue analgesia was significantly shorter in ropivacaine + dexmedetomidine group than that in ropivacaine control group, while the mean time for the 1st to 3rd rescue analgesia was significantly longer in ropivacaine + dexmedetomidine group than that in ropivacaine control group, showing statistically significant differences ($\chi^2$ = 15.31, p = 0.0005, $I^2$ = 87%). It can be seen that the mean time for rescue analgesia is decreased under ropivacaine combined with dexmedetomidine compared with that under ropivacaine.

### VAS score

The VAS score of parturients was reported in five studies, the results belonged to continuous data, and REM was used ($I^2$ > 50%) (Supplementary data Fig. S5). The results manifested that the VAS score at T1-T4 was significantly lower in ropivacaine + dexmedetomidine group than that in ropivacaine control group, showing a statistically significant difference ($\chi^2$ = 66.68, p < 0.001, $I^2$ = 96%; $\chi^2$ = 54.85, p < 0.001, $I^2$ = 95%; $\chi^2$ = 16.59, p = 0.002, $I^2$ = 88%; $\chi^2$ = 11.86, p = 0.003, $I^2$ = 83%). It can be seen that the VAS score obviously declines under ropivacaine combined with dexmedetomidine compared with that under ropivacaine.

### 24 h mean cumulative dose for rescue analgesia

The 24 h mean cumulative dose for rescue analgesia of parturients was reported in one study, and the results belonged to continuous data (Supplementary data Fig. S6). It was found that the 24 h mean cumulative dose for rescue analgesia was significantly lower in ropivacaine + dexmedetomidine group than that in ropivacaine control group, displaying a statistically significant difference (p < 0.001). It can be seen that the 24 h mean cumulative dose for rescue analgesia obviously declines under ropivacaine combined with dexmedetomidine compared with that under ropivacaine.

### Pain-free duration

The pain-free duration of parturients was reported in one study, and the results belonged to continuous data (Supplementary data Fig. S7). It was found that the pain-free duration was significantly longer in ropivacaine + dexmedetomidine group than that in ropivacaine control group, and the difference was statistically significant (p < 0.001). It can be seen that the pain-free duration is prolonged and the prognosis is good under ropivacaine combined with dexmedetomidine compared with those under ropivacaine.

### Time to first analgesia required

The time to first analgesia required was reported in one study, and the results belonged to continuous data (Supplementary data Fig. S8). It was found that the time to first analgesia required was significantly later in ropivacaine + dexmedetomidine group than that in ropivacaine control group, and the difference was statistically significant (p < 0.001). It can be seen that the time to first analgesia required is later and parturients have milder pain under ropivacaine combined with dexmedetomidine than those under ropivacaine.

### Ramsay sedation score

The Ramsay sedation score of parturients was reported in two studies, the results belonged to continuous data, and REM was used ($I^2$ > 50) (Supplementary data Fig. S9). It was found that the Ramsay sedation score at T1-T2 was significantly better in ropivacaine + dexmedetomidine group than that in

ropivacaine control group, and the difference was statistically significant ($\chi^2$ = 12.36, p < 0.001, $I^2$ = 92%; $\chi^2$ = 102.53, p < 0.001, $I^2$ = 99%), indicating that the Ramsay sedation score greatly rises and the prognosis is good under ropivacaine combined with dexmedetomidine compared with those under ropivacaine.

### *MMSE score*

The MMSE score of parturients was reported in 1 study, the results belonged to continuous data, and REM was used ($I^2$ > 50) (Supplementary data Fig. S10). The results showed that the MMSE score after 1 d was significantly superior in ropivacaine + dexmedetomidine group to that in ropivacaine control group, and the difference was statistically significant ($\chi^2$ = 67.60, p < 0.001, $I^2$ = 99%), indicating that the MMSE score after 1 d greatly rises and the prognosis is good under ropivacaine combined with dexmedetomidine compared with those under ropivacaine.

## Discussion

All the seven included studies had a small sample size (< 200 cases), so false-positive or false-negative results caused by random errors could not be excluded.

Several outcome indices were selected from the seven literatures, including the number of parturients in need of rescue, adverse reactions, satisfaction, incidence rate of TNS, visceral respiratory response, satisfaction with muscle relaxation, spinal anesthesia grade, mean time for rescue analgesia, VAS score, 24 h mean cumulative dose for rescue analgesia, pain-free duration, time to first analgesia required, Ramsay sedation score, and MMSE score[12-18]. The authenticity and reliability of the above outcome indices were assessed using the RevMan software.

The randomization method was known in all of the seven included studies. The allocation concealment was known in two studies and unknown in the remaining five studies. The blind method for subjects was unknown in three studies, and the blind method for result assessment was unknown in two studies. The outcome indices were incomplete in one study, and the selective reporting was high risk in one study and also unknown in one study.

The number of parturients in need of rescue, adverse reactions, satisfaction, incidence rate of TNS, visceral respiratory response, satisfaction with muscle relaxation, and spinal anesthesia grade were all two-category data. The results showed that ropivacaine + dexmedetomidine group had a significantly smaller number of parturients in need of rescue, those with visceral respiratory response in grade 2 and 3 and those receiving spinal anesthesia in grade 2 and 3, and significantly lower incidence rates of adverse reactions and TNS than ropivacaine control group, while ropivacaine + dexmedetomidine group had a significantly larger number of parturients with excellent satisfaction and significantly better satisfaction with muscle relaxation than ropivacaine control group. It can be seen that ropivacaine combined with dexmedetomidine can significantly improve the prognosis and satisfaction of parturients receiving cesarean section and reduce the incidence rate of clinical adverse reactions.

The mean time for rescue analgesia, VAS score, 24 h mean cumulative dose for rescue analgesia, pain-free duration, time to first analgesia required, Ramsay sedation score, and MMSE score were all continuous data. The results revealed that the mean time for the 4$^{th}$ and 5$^{th}$ rescue analgesia was significantly shorter, the VAS score at T1-T4 and 24 h mean cumulative dose for rescue analgesia were significantly lower, and the time to first analgesia required was significantly later in ropivacaine + dexmedetomidine group than those in ropivacaine control group, while the Ramsay sedation score at T1-T2 and MMSE score after 1 d were significantly superior in ropivacaine + dexmedetomidine group to those in ropivacaine control group. The above findings demonstrate that parturients in ropivacaine + dexmedetomidine group had milder pain, a better prognosis and a significantly better mental state than those in ropivacaine control group.

Nevertheless, this study is limited. The number of patients is small. In addition, the results between many studies are not compared, which may have a negative impact on the conclusion.

## Conclusions

Ropivacaine combined with dexmedetomidine has a better prognostic effect and causes fewer adverse reactions in parturients receiving cesarean section under anesthesia. The meta-analysis results remain to be improved with larger-sample higher-quality studies.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols. The study does not involve patient personal data.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

This study approved by Ningxia Armed Police Corps Hospital.

## Supplementary data

Supplementary data are available at DOI: 10.24875/CIRU.23000532. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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