Combination of sufentanil, dexmedetomidine and ropivacaine to improve epidural labor analgesia effect: A randomized controlled trial

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Abstract. Opioids and α2-agonists have been used as epidural adjuvants in local anesthetics for a long time, but the effect of the combination of opioids and α2-agonists as epidural adjuvants is not completely understood. In the present study, the combination of dexmedetomidine (Dex) and sufentanil as adjuvants to ropivacaine for epidural labor analgesia was investigated. A total of 108 parturient women receiving labor epidural analgesia were randomly divided into three groups: i) Group RD received 0.1% ropivacaine + 0.5 μg/ml Dex; ii) Group RS received 0.1% ropivacaine + 0.5 μg/ml sufentanil; and iv) Group RDS received 0.1% ropivacaine + 0.25 μg/ml Dex + 0.25 μg/ml sufentanil. Patients received a 10 ml loading dose followed by a maintenance by patient controlled epidural analgesia. The visual analog scale scores, onset time, local anesthetic requirements, motor blockage and adverse effects were recorded. Group RDS displayed an improved labor analgesia effect compared with Groups RD and RS. Group RDS displayed a shorter onset time compared with Groups RD and RS, and a reduced local anesthetic requirement compared with Group RS. The motor blockage in Groups RDS and RS was significantly lower compared with Group RD, and the incidence of pruritus in Groups RDS and RD was lower compared with Group RS. In conclusion, the combined use of 0.25 μg/ml Dex and 0.25 μg/ml sufentanil as adjuvants to 0.1% ropivacaine for epidural labor analgesia displayed an improved analgesia effect compared with the use of either 0.5 μg/ml sufentanil or 0.5 μg/ml Dex alone. The present study was registered with the Chinese Clinical Trial Registry Center on 23 February, 2018 (registration no. ChiCTR-IOR-1800014943).

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Introduction

Delivery pain has been reported to be one of the most painful experiences of the majority of women, which can cause potential harm to both the mother and the baby (1-3). Epidural blockade is the most effective method of labor analgesia, which facilitates painless labor and can be customized for each patient (4). However, there are also a number of disadvantages associated with epidural labor analgesia, including motor blockade, a lengthened second stage of labor and hypotension (5). Anesthetists have been seeking strategies to improve the effects of analgesia and avoid the aforementioned side effects, and the use of opioids and α2-adrenoreceptor agonists as adjuvant drugs is an example (6,7).

Sufentanil and dexmedetomidine (Dex) have been used individually as adjuvants to ropivacaine for epidural labor analgesia to alleviate the side effects. Debon *et al* (8) reported that the use of sufentanil as an adjuvant increased the duration of epidural labor analgesia. The use of opioids as adjuvants results in a high incidence of respiratory depression, urinary retention, nausea, vomiting and pruritus. The safety of epidural and spinal administration of Dex has been demonstrated in humans, where epidural administration was hypothesized to block sympathetic nerve slower and therefore, increased safely (9,10). Compared with ropivacaine alone, the addition of Dex as an adjuvant to epidural ropivacaine can reduce the feeling of pain, but does not result in motor blockage (11). In addition, Zhang *et al* (12) reported that the analgesic effect and duration of the first stage of labor during epidural analgesia (EA) with 0.1% ropivacaine + Dex was superior compared with 0.1% ropivacaine + sufentanil. In previous studies, intrathecal Dex lengthened the sensory and motor blockage during hysteroscopic surgery and cesarean sections (13,14). Therefore, it has been hypothesized that the combination of Dex and sufentanil as epidural adjuvants could enhance the

beneficial effects of each adjuvant. To the best of our knowledge, the present study investigated for the first time whether the combination of Dex and sufentanil in labor analgesia could improve the effects of analgesia and decrease the incidence of associated side effects. The results of the present study may provide insight into epidural blockade and provide a novel strategy for labor analgesia.

Materials and methods

Study subjects. The present randomized, double-blinded, prospective, controlled trial was performed at Shenzhen Maternity and Child Healthcare Hospital, Southern Medical University. The present study was approved by the Shenzhen Maternity and Child Healthcare Hospital Ethics Committee (approval no. SZFY2018020798).

All parturient women undergoing vaginal delivery and requesting labor analgesia in the hospital between March 2018 and October 2018 were considered for inclusion. The inclusion criteria were as follows: i) Aged 20-35 years; ii) American Society of Anesthesiology Physical Status I/II (15); iii) a single fetus; iv) ≥37 gestation weeks; v) cervical dilatation of 3 cm; and vi) provided written informed consent. The exclusion criteria were as follows: i) Refusal to participate; ii) aged <18 years; iii) endocrine diseases, obesity, hypertension or hypotension; iv) fetal compromise; v) allergy to study agents; or vi) an inability to communicate. Furthermore, if the epidural anesthesia failed, the epidural catheter was dislodged, an inadvertent epidural puncture occurred or a rapid progress in labor occurred (delivery in <120 min), the patient was excluded from the final analysis.

Group allocation. Written informed consent was obtained from all included parturient women. A total of 108 parturient women were assigned to three groups: i) Group RD received 0.1% ropivacaine + 0.5 μg/ml Dex; ii) Group RS received 0.1% ropivacaine + 0.5 μg/ml sufentanil; and iv) Group RDS received 0.1% ropivacaine + 0.25 μg/ml Dex + 0.25 μg/ml sufentanil. All treatments were administered by epidural injection.

Parturient women were randomly assigned to the three treatment groups by an independent investigator using a computer-generated random number table. The grouping assignment was sealed in envelopes and not opened until just before the anesthesia was administered. To maintain blinding, the investigators and patients were not informed of the group assignments.

Sample size. Based on the preliminary data (data not shown), the visual analog scale (VAS) score (16) at 10 min after epidural placement [mean (standard deviation)] in the RS group was 5.0 (2.5), which was reduced to 3.7 (2.1) in the RDS group. By setting the VAS score as the primary variable, 30 patients were assigned to each group with a statistical significance of 0.05 and a power of 90%. To compensate for possible dropouts or excluded cases, 36 parturient women were assigned to each group.

Procedures. To eliminate any possible effects of anesthetic technique, the same anesthetist group performed all procedures. When cervical dilatation reached 3 cm, EA was performed at the L2/L3 intervertebral space using a 16G epidural needle to insert an epidural catheter 3-4 cm into the epidural space. Following the administration of a test dose of 3 ml 1% lidocaine for 5 min, parturients received 10 ml 0.5 μg/ml Dex (Group RD), 0.5 μg/ml sufentanil (Group RS) or 0.25 μg/ml Dex + 0.25 μg/ml sufentanil (Group RDS), together with 0.1% ropivacaine as the loading dose. The maintenance of patient controlled EA was administered after the loading dose using an Apon PCA pump (Jiangsu Apon Medical Technology Co., Ltd.). The pumps were set at a rate of 7 ml/h with a rescue bolus of 7 ml (lockout 25 min; limit 25 ml/h). Patients experiencing inadequate analgesia could request an additional 5 ml bolus of the medication solution, via epidural administration by the nurse.

If hypotension (90/60 mmHg) occurred, the patient was placed in a left-leaning position or phenylephrine was administered as a vasoconstrictor active drug. After delivery, the administration of the drugs was terminated and the epidural catheter was removed.

Data collection. The demographic and baseline measurements, including age, height, weight and gestational age, were recorded. In the present study, the VAS score (0, no pain; 10, most serious pain) was evaluated prior to epidural placement (baseline) and at 5, 10, 20, 30, 60, 90 and 120 min after the loading dose was injected. The administration of the loading dose was considered to be 0 min. The time of onset, which was defined as the duration between the end of drug administration and the patient displaying a VAS score <3, was observed. The duration of each labor period (active period, second stage and third stage), Apgar score (11), umbilical vein pH, cesarean delivery rate, bolus frequency and total volume of anesthetic solution were also recorded. Evaluation of motor blockage was conducted using the Bromage scoring system (1, able to lift the legs above the table; 2, able to bend the knees; 3, able to move the feet only; 4, no movement in the feet or legs) (7). Additionally, hypotension (systolic blood pressure <90 mmHg or <30% of the base value), bradycardia (heart rate <60 bpm), nausea, vomiting, shivering and pruritus were monitored.

In the present study, the primary outcome was the VAS score, and the secondary outcomes were the onset time, duration of each labor stage, Apgar score, cesarean delivery rate, bolus frequency, total volume of anesthetic solution, Bromage score and other side effects.

Statistical analysis. Statistical analyses were conducted using SPSS software (version 20.0; IBM Corp.). The one-sample Kolmogorov-Smirnov test was used to assess the normality of the quantitative data. Quantitative variables are presented as the mean ± standard deviation and categorical variables are presented as numbers (%; n, %). Quantitative variables were analyzed using one-way ANOVA followed by the Bonferroni post hoc test. Categorical variables were analyzed using the χ^2 test or Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient variables. A total of 108 parturient women were recruited into the present study; however, one woman was excluded during the study due to a protocol deviation resulting in a suspected

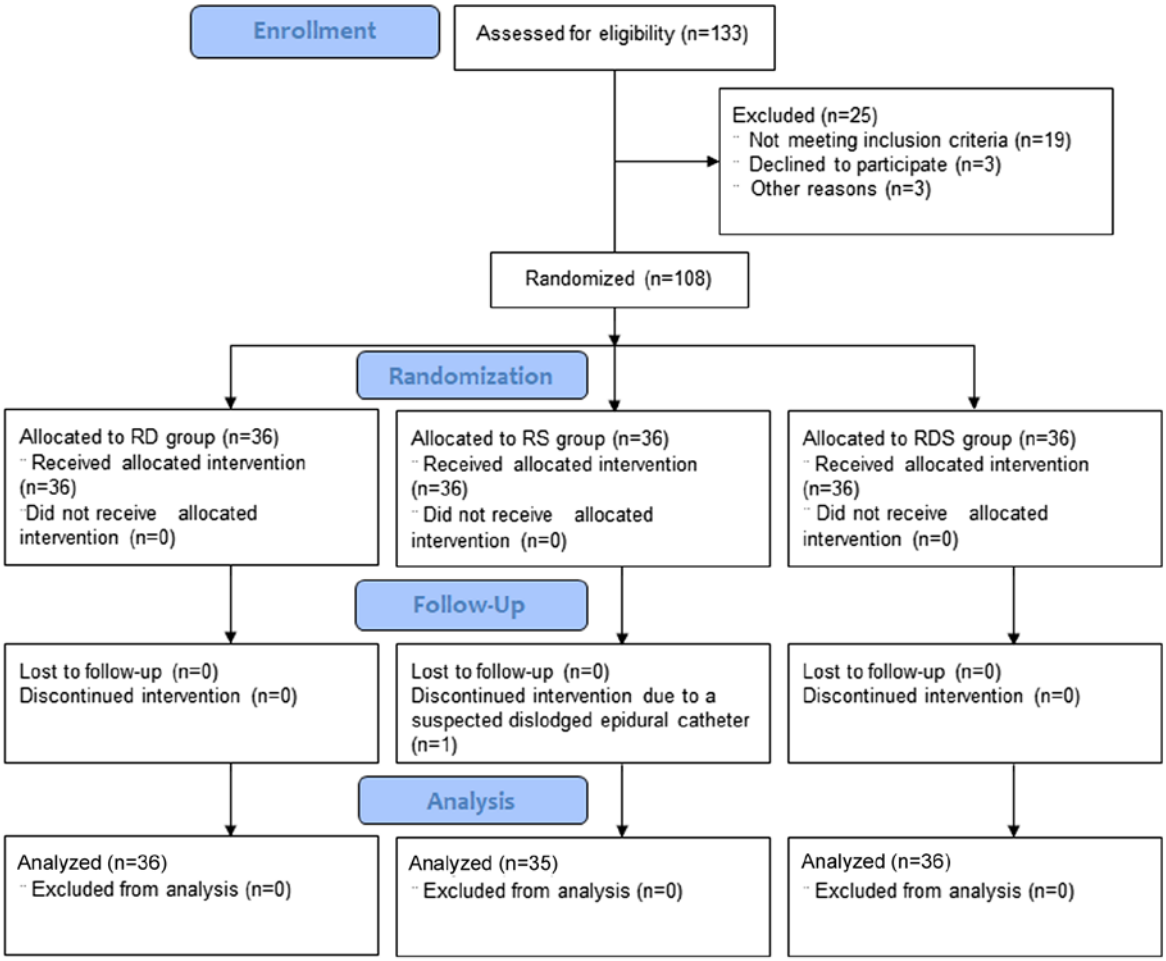

Figure 1. Consolidated Standards of Reporting Trials flow chart. Blue boxes represent the committed step of the clinical trial. RS, sufentanil + ropivacaine epidural; RD, dexmedetomidine + ropivacaine epidural; RDS, dexmedetomidine + sufentanil + ropivacaine epidural.

dislodged epidural catheter. Therefore, 107 parturient women were included in the final analysis among the RD, RS and RDS groups (Fig. 1). The demographic variables of the parturient women in the three groups were comparable, including age, height, weight and gestational age (P>0.05; Table I).

Primary outcomes. The VAS scores at 10 min after epidural placement in Groups RDS (2.44±1.27 vs. 5.13±2.74; P<0.001) and RD (3.67±2.71 vs. 5.13±2.74; P<0.05) were significantly decreased compared with Group RS (Table II). Furthermore, at the 5, 10, 20, 30, 60, 90 and 120 min time points, Group RDS displayed significantly lower VAS scores compared with Group RS (P<0.05; Table II and Fig. 2). In addition, the VAS scores in Group RDS were significantly lower compared with Group RD at 20 and 30 min (P<0.05; Table II and Fig. 2). Group RD also displayed significantly lower VAS scores compared with Group RS at 10, 60, 90 and 120 min (P<0.05; Table II and Fig. 2).

Secondary outcomes. The parturient women in the three groups were comparable for the following factors: Duration of each labor stage, Apgar scores, umbilical vein pH and cesarean delivery rate (P>0.05; Table III). In addition, no patient experienced inadequate analgesia; therefore, the additional 5 ml bolus analgesia was not administered to any of the patients.

The onset time of Group RDS was significantly shorter compared with Groups RS and RD (P<0.05), and the parturient women in Groups RDS and RD required a reduced injection volume and fewer local anesthetic administrations compared with Group RS (P<0.05; Table IV). Motor blockage in Group RD was more severe compared with Groups RS (9/19/2/0 vs. 27/2/1/0; P<0.001) and RDS (9/19/2/0 vs. 22/8/0/0; P<0.001; Table IV). Additionally, the incidence of pruritus was significantly lower in Groups RD and RDS compared with Group RS (P<0.05; Table V).

There were no statistical differences in the proportion of patients with nausea, vomiting, shivering, bradycardia, hypotension and urinary retention among the three groups (P>0.05; Table V).

Discussion

Labor pain is a complicated sensory reaction that occurs during delivery. EA with local anesthetics is the main strategy used to induce labor analgesia, and the most representative adjuvants used in clinical practice for labor analgesia are opioids and α2-adrenergic receptor agonists (17,18). Compared with the use of 0.1% ropivacaine + 0.5 μg/ml Dex or 0.5 μg/ml sufentanil, 0.1% ropivacaine in combination with 0.25 μg/ml Dex and 0.25 μg/ml sufentanil resulted in an improved labor

Table I. Demographic baseline variables.

Variable	Group RS (n=35)	Group RD (n=36)	Group RDS (n=36)	P-value
Age (years)	30.13±4.86	29.23±3.88	30.83±3.77	0.340
Height (cm)	159.03±4.49	159.61±5.13	159.70±4.42	0.829
Weight (kg)	64.73±8.85	65.21±7.15	66.35±9.01	0.756
Gestational age (weeks)	37.41±3.94	39.10±0.91	38.22±2.92	0.063

Data are presented as the mean ± SD. Patients were randomly assigned to the three groups. RS, sufentanil + ropivacaine epidural; RD, dexmedetomidine + ropivacaine epidural; RDS, dexmedetomidine + sufentanil + ropivacaine epidural.

Table II. Visual Analog scale at different time points.

Time (min)	Group RS (n=35)	Group RD (n=36)	Group RDS (n=36)	P-value
Baseline	8.90±1.60	8.81±1.54	8.69±1.15	0.822
5	6.72±2.33	5.71±3.33	5.35±1.72[a]	0.103
10	5.13±2.74	3.67±2.71[a]	2.44±1.27[b]	0.000
20	2.99±1.44	2.87±1.53	1.84±1.15[a,c]	0.013
30	2.98±1.75	2.80±2.16	1.72±1.07[a,c]	0.011
60	3.46±2.18	2.17±1.24[a]	1.75±1.17[a]	0.004
90	3.11±1.68	2.20±1.51[a]	1.74±1.22[a]	0.009
120	3.46±1.47	2.23±1.40[a]	1.53±1.05[b]	0.000

Data are presented as the mean ± SD. Patients were randomly assigned to the three groups. [a]P<0.05 and [b]P<0.001 vs. Group RS. [c]P<0.05 vs. Group RD. RS, sufentanil + ropivacaine epidural; RD, dexmedetomidine + ropivacaine epidural; RDS, dexmedetomidine + sufentanil + ropivacaine epidural.

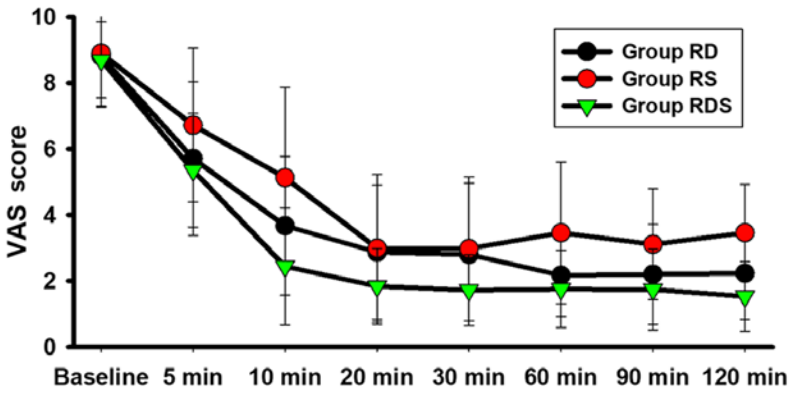

Figure 2. VAS among the three groups. Data are presented as the mean ± SD. Patients were randomly assigned to the three groups. The VAS score (0, no pain; 10, most serious pain) was evaluated before epidural placement (baseline), and 5, 10, 20, 30, 60, 90 and 120 min after the loading dose was injected, which was considered to be 0 min. VAS, Visual Analog Scale; RS, sufentanil + ropivacaine epidural; RD, dexmedetomidine + ropivacaine epidural; RDS, dexmedetomidine + sufentanil + ropivacaine epidural.

analgesia effect, quicker onset time, reduced need for local anesthetics and fewer side effects.

Sufentanil has been used as local anesthetic adjuvant in epidural labor analgesia in a number of previous studies (1,12); therefore, sufentanil in combination with ropivacaine was used as the positive control in the present study. Dex has also been reported to display hemodynamic stability, pain alleviation, improved stress responses without respiratory depression when administered intravenously and intratracheally (19,20), and improved epidural and neuraxial blocks (21,22). Zhao *et al* (11) reported that compared with ropivacaine alone, the addition of Dex to epidural ropivacaine reduced the feeling of pain and did not result in motor blockage. Abdallah *et al* (23) also reported that both perineural and intravenous Dex effectively prolonged the interscalene brachial plexus block analgesic duration

Table III. Data of parturient women and neonatal outcome.

Variable	Group RS (n=35)	Group RD (n=36)	Group RDS (n=36)	P-value
Duration of the first labor stage (min)	396.11±14.56	347.93±10.15	396.26±9.37	0.819
Duration of the second labor stage (min)	30.59±7.67	52.54±6.49	42.74±6.799	0.127
Duration of the third labor stage (min)	10.92±6.38	10.46±7.82	11.59±10.07	0.879
Apgar score[a]				
1 min ≥7	35 (100)	36 (100)	36 (100)	1.000
5 min ≥9	35 (100)	36 (100)	36 (100)	1.000
Umbilical vein pH	7.21±0.08	7.21±0.02	7.20±0.05	0.793
Cesarean delivery (%)	13.3	10.0	10.0	0.897

[a]Apgar Score was measured twice for each of the newborns-once after 1 min, and again at 5 min. Data are presented as the mean ± SD or number (%). Patients were randomly assigned to the three groups. RS, sufentanil + ropivacaine epidural; RD, dexmedetomidine + ropivacaine epidural; RDS, dexmedetomidine + sufentanil + ropivacaine epidural.

Table IV. Onset time, local anesthetic requirement and Bromage score.

Variable	Group RS (n=35)	Group RD (n=36)	Group RDS (n=36)	P-value
Onset time (min)	15.50±2.67	12.97±3.13	9.68±1.26[a,c]	0.037
Total volume of anesthetic solution (ml)	65.44±5.64	42.65±6.44	50.34±6.56[a]	0.043
Bolus frequency	2.80±0.92	0.10±0.31[a]	0.80±0.78[a]	0.026
Bromage score (1/2/3/4)	27/2/1/0	9/19/2/0[b]	22/8/0/0[d]	0.000

Data are presented as the mean ± SD or number. Patients were randomly assigned to the three groups. [a]P<0.05 and [b]P<0.001 vs. Group RS. [c]P<0.05 and [d]P<0.001 vs. Group RD. RS, sufentanil + ropivacaine epidural; RD, dexmedetomidine + ropivacaine epidural; RDS, dexmedetomidine + sufentanil + ropivacaine epidural.

Table V. Adverse events among the three groups.

Event	Group RS (n=35) (%)	Group RD (n-36) (%)	Group RDS (n=36) (%)	P-value
Hypotension	0 (0.0)	1 (2.8)	0 (0.0)	1.000
Bradycardia	0 (0.0)	1 (2.8)	0 (0.0)	1.000
Nausea	1 (2.9)	0 (0.0)	0 (0.0)	0.327
Vomiting	1 (2.9)	1 (2.8)	0 (0.0)	0.771
Shivering	2 (5.7)	3 (8.3)	2 (5.6)	1.000
Pruritus	5 (14.3)	0 (0.0)[a]	0 (0.0)[a]	0.003
Urinary retention	2 (5.7)	2 (5.6)	1 (2.8)	0.869

Data are presented as the number (%). Patients were randomly assigned to the three groups. [a]P<0.05 vs. Group RS. RS, sufentanil + ropivacaine epidural; RD, dexmedetomidine + ropivacaine epidural; RDS, dexmedetomidine + sufentanil + ropivacaine epidural.

and reduced sufentanil consumption without prolonging motor blockade. By contrast, certain studies have indicated that intrathecal Dex lengthens sensory and motor blockage during hysteroscopic surgery and cesarean sections (13,14), and the addition of epidural opioids results in a high incidence of respiratory depression, urinary retention, nausea, vomiting and pruritus (24,25). Qin *et al* (26) also reported that the combination of Dex and sufentanil for postoperative analgesia in patients with partial laryngectomy resulted in significantly reduced sufentanil consumption, improved analgesia, a reduced frequency of coughing episodes and improved sleep quality. To the best of our knowledge, the present study was the first study to investigate the combination of epidural Dex and sufentanil in labor analgesia. In the present study, Group RDS displayed lower VAS scores compared with Group RS at all time points, and compared with Group RD at 20 and 30 min after epidural placement. The results indicated that the combined administration of Dex and sufentanil as adjuvants to local anesthetic displayed an improved analgesic effect compared with the use of either drug alone.

Both 0.5 μg/ml Dex and 0.5 μg/ml sufentanil have been used as adjuvants in clinical practice (12,27). In the present study, the combination of 0.25 μg/ml Dex + 0.25 μg/ml sufentanil + 0.1% ropivacaine was administered via an epidural for labor analgesia, and the efficiency and safety of the combined treatment was compared with 0.1% ropivacaine + 0.5 μg/ml Dex or 0.5 μg/ml sufentanil. The dose used in the present study was determined according to a preliminary study, which indicated that for epidural labor analgesia the optimal concentration of Dex was 0.5 μg/ml when combined with 0.1% ropivacaine;

therefore, 0.5 μg/ml Dex was used as an adjuvant to epidural ropivacaine in labor analgesia. Furthermore, the addition of 5 μg intrathecal Dex to 10 μg fentanyl lengthened the analgesia duration and lowered the incidence of adverse effects compared with the use of intrathecal 10 μg Dex or intrathecal 20 μg fentanyl alone (28). Therefore, 0.25 μg/ml Dex and 0.25 μg/ml sufentanil were used as adjuvants in combination with 0.1% ropivacaine epidurally for labor analgesia in the present study.

Koraki *et al* (29) reported that the onset time of epidural Dex combined with ropivacaine was ~15 min, which was longer compared with the results of the present study. The inconsistency could be explained by the different ropivacaine concentrations used in each study. The combined use of ropivacaine, 0.25 μg/ml Dex and 0.25 μg/ml sufentanil displayed a quicker onset time, enhanced the analgesic effect, decreased the VAS scores, reduced the bolus frequency and limited motor blockage without causing adverse side effects compared with the use of either adjuvants alone. The results indicated that Dex synergized with sufentanil systemically and regionally, which was consistent with previously reported clinical results (26,30).

The analgesic effect of Dex is not completely understood. Eisenach *et al* (31) reported that Dex is present in the cerebrospinal fluid rapidly after administration and binds highly to α2-receptors in the spinal cord. Marhofer *et al* (32) demonstrated that the analgesic effect of Dex was primarily mediated at the spinal level; therefore, epidural administration is recommended. Yang *et al* (33) reported that intraperitoneal Dex displayed a dose-dependent analgesic effect by inhibiting hyperpolarization-activated cyclic nucleotide-gated currents. Recently, Sun *et al* (34) reported that the analgesic effects of Dex were associated with its anti-inflammatory effect. The aforementioned studies indicated that Dex exerts analgesic effects not only via α2-adrenergic receptors, but also by direct channel inhibition via an α2-independent mechanism, which enables Dex to serve as an analgesic adjuvant. A recent systematic review and meta-analysis demonstrated that the use of Dex as an adjuvant in epidural procedures is generally safe and well tolerated (35).

Compared with the combination of Dex and sufentanil, 0.5 μg/ml epidural Dex weakened muscle strength and induced more severe motor block, which was consistent with previous studies (13,14). Furthermore, the incidence of pruritus observed in the present study was similar to the incidence reported by Boselli *et al* (36). No significant intergroup differences were detected for the three stages of labor, umbilical vein pH or Apgar scores, which was consistent with previous studies (7,37,38).

The present study had a number of limitations. Firstly, the present study only investigated the efficiency and safety of 0.25 μg/ml Dex and 0.25 μg/ml sufentanil as adjuvants to 0.1% ropivacaine; therefore, further studies should be performed using different doses of epidural Dex and sufentanil. Secondly, the present study was a single-center clinical trial and the preliminary results should be verified by a large-scale multicenter study. Thirdly, although Dex has been widely used as an epidural drug in clinical practice and has been reported to display no significant adverse reactions, it is still not licensed for epidural use. In particular, the safety of Dex needs to be investigated in a large-scale phase IV clinical trial. Finally, the Ramsay sedation scale (39) was not assessed in the present study; therefore the effect of Dex on the sedative state of an individual requires further investigation.

In summary, the present study investigated the effects of using 0.25 μg/ml Dex and 0.25 μg/ml sufentanil as adjuvants to 0.1% ropivacaine for labor analgesia. The combined adjuvant group displayed an improved analgesia effect, quicker onset time, reduced need for local anesthetics and decreased rate of pruritus compared with sufentanil (0.5 μg/ml). In addition, compared with Dex (0.5 μg/ml), the combined adjuvant group displayed reduced motor blockage. However, Dex is not licensed for epidural use and its safety requires further investigation. The results of the present study indicated that the combined use of Dex and sufentanil increased the effectiveness of the local anesthetic agent during epidural labor.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request

Authors' contributions

YUL designed and supervised the study. GL, YX, XW, JS and YOL conducted the study and collected the data. XQ and HW performed the data analysis. GL wrote the paper. XW, JS and YOL help revised the manuscript. GL and YX contributed equally to the work. All authors read and approved the final manuscript.

Ethical approval and consent to participate

The present study was approved by the Shenzhen Maternity and Child Healthcare Hospital Ethics Committee (approval no. SZFY2018020798) and registered with the Chinese Clinical Trial Registry Center on Feb 23, 2018 (registration no. ChiCTR-IOR-1800014943). Written informed consent was obtained from all parturient women.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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