

INTRATHECAL DEXMEDETOMIDINE AS AN ADJUVANT TO BUPIVACAINE FOR SPINAL ANAESTHESIA FOR ELECTIVE CESAREAN SECTION: A RANDOMISED DOUBLE-BLIND CONTROLLED STUDY

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Abstract: Objective: This study was designed to evaluate dexmedetomidine (Dex) 5ug as adjuvant combined with 0.5% bupivacaine 10 mg in elective Lower segment cesarean section (LSCS) with respect to the effect on parturients and newborns. Methods: Eighty parturients (ASAI-II) undergoing elective LSCS were assigned to 2 groups (n=40) to receive either 0.5% bupivacaine 10 mg with saline (Group C) or 0.5% bupivacaine 10mg with Dex 5ug (Group D). Adverse effects, hemodynamic parameters, Ramsay scores, VAS scores and neonatal Apgar scores were recorded. Umbilical artery blood was collected for blood gas analysis and measuring the levels of umbilical artery blood catecholamine. Data obtained were compiled and analyzed with appropriate tests, $p < 0.05$ was considered significant. Results: Compared with group C, the VAS score of group D was significant lower at T4 ($p < 0.05$); The incidence rates of Chill, Nausea, vomit of group D were lower than that in group C ($p < 0.05$); This study revealed that the levels of umbilical artery blood lactic acid(Lac), Epinephrine (EPI) and Norepinephrine (NA) of group D were obvious lower than that in group C ($p < 0.05$); MAP, HR, SPO₂, Apgar score and Ramsay score did not show statistical difference between the two groups. Conclusions: The addition of 5ug Dex as an intrathecal adjuvant to bupivacaine for elective LSCS provides better analgesia without significant adverse effects, and also reduce the incidence of chill, nausea, vomit during operation.

Keywords: Dexmedetomidine; Bupivacaine; Intrathecal; Lower segment cesarean section.

INTRODUCTION

Combined spinal and epidural anesthesia(CSEA) for elective LSCS continues to be the technique favoured by most anesthesiologists due to its safety and reliability, rapid onset and muscle relaxation, and it was considered be an ideal choice for

LSCS when there are no contraindications to this technique [1]. In order to ensure the LSCS was performed without maternal discomfort, blockade to T4 dermatome is necessary, such a high level always associated with hypotension and uterine placenta hypoperfusion. It make sense to take low doses local anesthetics to avoid hypotension but carries a risk of limited

duration and lack of intraoperative analgesia. To overcome this disadvantage, Some drugs (fentanyl, sufentanil, epinephrine, etc.) have been used as adjuvants in spinal anesthesia [2-5].

Dex is a highly selective α_2 adrenergic receptor agonist with many properties such as sedative, analgesic, perioperative sympatholytic and hemodynamic stabilizing, and it has been used as an adjuvant for subarachnoid block in lower abdominal surgical procedures and lower limb surgery [6] to extend the duration of analgesia of local anaesthetic in spinal. The purpose of this study was to compare the effect on parturients and newborns followed by intrathecal bupivacaine vs. intrathecal bupivacaine supplemented with 5ug Dex.

POPULATIONS AND METHODS

POPULATIONS

All the subjects of this study were from the maternity ward of The First affiliated Hospital of JNU. The study obtained the informed consent of patients and their families, and was approved by the ethics committee of The First affiliated Hospital of JNU.

This prospective study concludes 80 parturients who undergoing elective LSCS. The 80 subjects were randomly divided into two groups with 40 parturients (n=40) in each group. Inclusion criteria included that: 1. American Society of Anesthesiologists grade 1 and 2; 2. Undergoing elective LSCS under CSEA; 3. there was no obvious abnormality in parturients and newborns. Exclusion criteria included that parturient with mental disease, neurological disease, motion sickness, diabetes; end organ affection in the form of hepatic, cardiovascular or renal impairment, parturient with a history of allergy to local anesthetics or drugs used in this study were also excluded. All operations were performed or supervised by the same surgical and anesthesia teams.

METHODS

The parturients in this study received routine institutional anesthesia car. On arrival to the operation room a 20G IV cannula was inserted on the dorsum of the

non-dominant hand. Standard anesthetic monitoring included an electrocardiogram (ECG), pulse oximetry and noninvasive arterial blood pressure (NIBP) was applied, respiratory rate measured via an oxygen delivery nasal cannula with oxygen supplement delivery at 3L/min.

The study drugs were prepared by the senior anesthesiologist who was not involved in further observations of the parturients. The parturients were placed in the left lateral decubitus position, and after aseptic precautions and numbing of the skin with 1% lidocaine, a 17-gauge Tuohy needle was placed at the L3/4 intervertebral space, after the epidural space was identified using the loss-resistance technique, a 25-gauge spinal needle was inserted, then 0.5% bupivacaine 10 mg with saline (Group C) or 0.5% bupivacaine 10mg with Dex 5ug (Group D) was injected into the subarachnoid space, After that, a catheter was inserted 5 cm in the cephalad direction. The parturients were then immediately turned to supine position, and then tilt the operating table to the left by 15° to prevent supine hypotension.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), maternal mean arterial pressure (MAP), heart rate (HR), SpO₂, Ramsay sedation score (Ramsay score) and Visual analogue pain score (VAS score) were recorded at before anesthesia (T1), 10 minutes after anesthesia (T2), beginning of surgery (T3), the time of delivery (T4) and before leaving the operating room (T5). Adverse reaction such as nausea, vomiting, chills and respiratory depression (respiration rate less than 10 bpm) during surgery were also recorded. Any reduction of SBP more than 20% below baseline or fall in SBP less than 90 mmHg was considered as hypotension and 10 mg of Ephedrine hydrochloride was intravenously injected if necessary, 0.2mg of Atropine was needed when the HR was less than 50 bpm. Neonatal Apgar scores were assessed by attending pediatrician at the first and fifth minute after delivery.

2 ml of blood samples from the umbilical artery of newborns were collected for blood gas analysis, and another 8 ml of blood samples for ELISA. Blood oxygen partial

pressure (PO₂), carbon dioxide partial pressure (PCO₂), pH, oxygen saturation (SO₂), lactate (Lac), plasma adrenaline and norepinephrine were recorded.

Statistical analysis:

All the data were analysed using Statistical Package for Social Science (SPSS) version 13.0. Descriptive statistics were used to summarize the data. Independent-Samples *t*-test and one-way ANOVA were used for

comparison between groups, and Chi-squared Test was used for Enumeration data. $p < 0.05$ was considered significant.

RESULTS

1. Population: The parturients in both groups were comparable with respect to demographic characteristics, and all the parturients completed the study, Table 1.

Table 1 The comparison of patient characteristics between group D and C ($\bar{X} \pm s$)

Group	n	Parturients			newborns
		age (yr)	height (cm)	weight (kg)	weight (kg)
C	40	28.8±1.4	158.2±5.6	68.8±3.0	3.5±1.6
D	40	27.5±0.8	160.4±2.1	67.7±2.7	3.4±0.8

2. Hemodynamics: The HR and MAP of the two groups at T2, T3, T4, and T5 showed a downward trend. However, there was no statistical difference in HR, MAP and SPO₂ between the two groups, Table 2.

Table 2 The comparison of hemodynamics between group D and C ($\bar{X} \pm s$)

Group	Variable	T1	T2	T3	T4	T5
C	HR (bpm)	82.8±4.2	82.4±4.2	68.0±3.7	72.6±3.9	75.0±5.0
	MAP (mmHg)	84.7±1.9	69.3±4.1	74.3±4.1	76.4±3.8	77.4±2.7
	SpO ₂ (%)	97.3±0.5	99.2±0.3	99.1±0.2	98.3±0.6	99.5±0.2
D	HR (bpm)	84.1±2.4	87.0±3.7	71.3±2.5	72.5±2.6	69.7±2.3
	MAP (mmHg)	88.3±3.0	71.6±5.8	84.0±3.8	73.2±4.2	75.6±1.9
	SpO ₂ (%)	97.1±0.2	99.3±0.1	99.0±0.3	98.6±0.3	99.4±0.1

3. VAS score and Ramsay score: VAS score of group D at T4 was significantly lower than that of group C ($p < 0.05$), Fig.1. The Ramsay score between the two groups at each point showed no significant difference, Fig.2.

4. Newborns: None of the newborns had respiratory depression, and there was no significant difference in Apgar score between the two groups at the first and fifth minute after delivery, Fig. 3.

5. Blood gas analysis: Lac in group D was significantly lower than that in group C ($p < 0.05$), Fig.4. There were no significant difference in pH, PO₂, PCO₂ and SO₂ between the two groups, Table 3.

6. The content of catecholamine in cord blood: ELISA showed that the content of EPI and NA in group D was significantly lower than that in group C ($p < 0.05$), Fig.5, Fig.6.

7. Incidence of adverse reactions: The incidence of chill, nausea and vomit in group D was significantly lower than that in group C ($p < 0.05$). No bradycardia or respiratory depression occurred in both groups, Table.4.

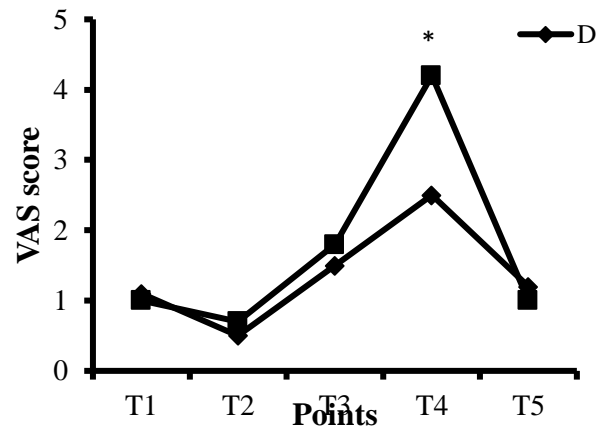


Fig. 1 The tendency chart of VAS score between groups D and C at each point * $p < 0.05$ vs group C

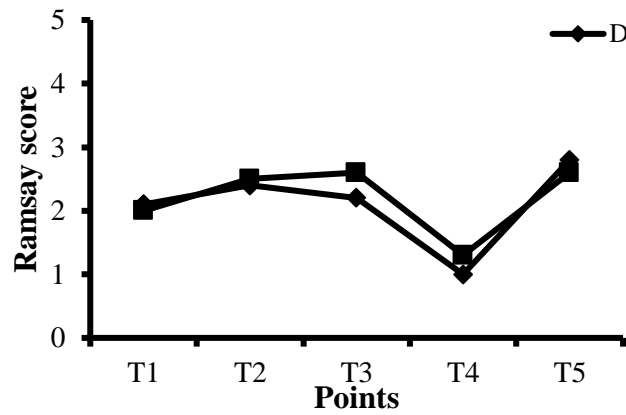


Fig. 2 The tendency chart of Ramsay score between group D and C at each point

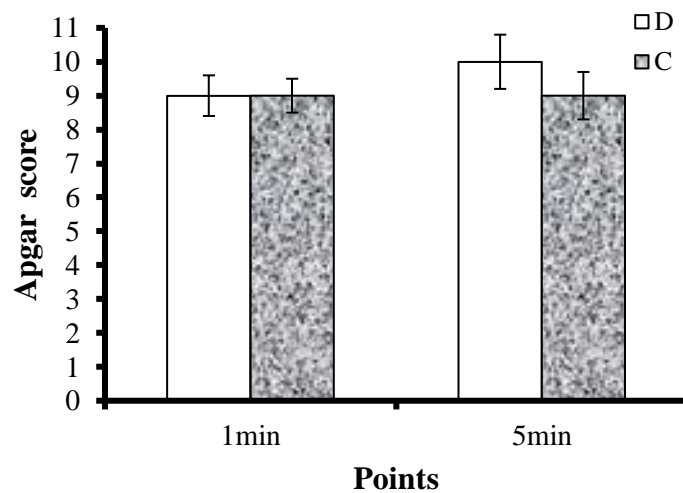


Fig. 3 The comparison of Apgar score between the two groups of newborns

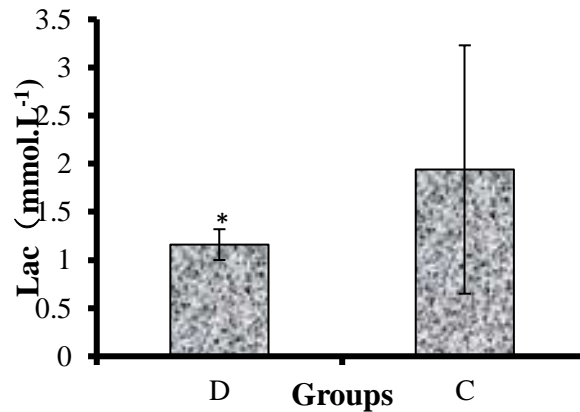


Fig. 4 The comparison of Lac content between the two groups of newborns * $p < 0.05$ vs group C

Table 3 The comparison of the neonatal cord blood gas analysis between group D and C ($\bar{X} \pm s$)

Group	PH	PO ₂ (mmHg)	PCO ₂ (mmHg)	SO ₂ (%)	Lac (mmol/L)
Group C	7.30±0.63	31.38±5.58	46.15±5.52	53.08±14.37	1.94±1.29*
Group D	7.32±0.04	32.55±4.97	45.90±6.12	56.93±12.55	1.16±0.16*

* $p < 0.05$ vs group C

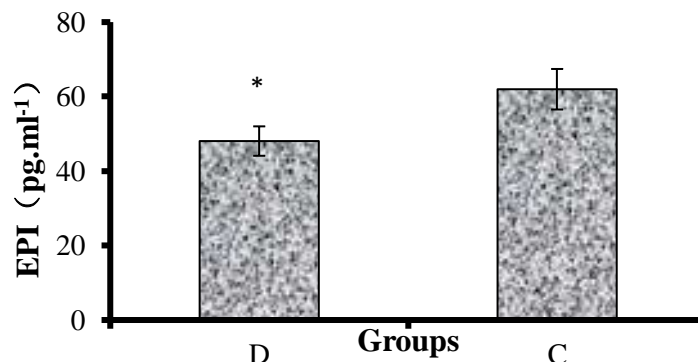


Fig. 5 The comparison of EPI content between the two groups of newborns * $p < 0.05$ vs group C

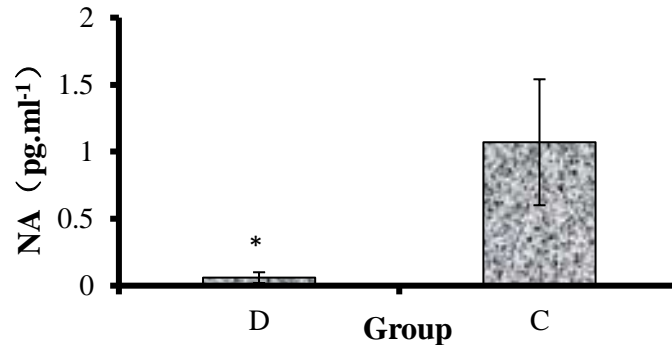


Fig. 6 The comparison of NA content between the two groups of newborns * $p < 0.05$ vs group C

Table 4 The comparison of Adverse effect between group D and C (case)

Group	Chills	Nausea	Vomiting	Bradycardi a	respiratory depression
Group D	5 (12.5%) *	4 (10.0%) *	2 (5.0%) *	0	0
Group C	14 (35.0%)	11 (27.5%)	8 (20.0%)	0	0

* $p < 0.05$ vs group

DISCUSSION

Dex is a potent $\alpha 2$ -adrenoceptor agonist with 8 time’s higher affinity for $\alpha 2$ -adrenoceptor than clonidine. There are many studies showing that Dex is a safe and effective adjuvant for lumbar anesthesia [7-10]. At present, the optimal dose of intrathecal Dex has not been established, an optimal intrathecal Dex dose necessary for sensory and motor blockade appears to be in between 2.5 μg and 10 μg , and with the increasing dose showed better and longer sensory and motor block [11]. In the current study, 5ug Dex was chosed as an intrathecal adjuvant based on several previous studies [12-14].

The safety of Dex as an adjuvant in spinal anaesthesia is the focuses which are paid wide attention in the medical field. Now a days, animal study has demonstrated that adding Dex to local anaesthetics used in spinal anaesthesia prolongs the duration of sensory and motor blockade without any neurotoxicity and histopathological[15,16]. In several clinical practice, no abnormal symptoms or signs in the nervous system were reported which suggest that Dex is a safe intrathecal adjuvant agent [11, 12, and 14]. Neumann reported that Dex could be detected in umbilical cord blood after intravenous infusion and affect Apgar score at 1-8 minutes after neonatal delivery [17], but other researchers found there was no significant effect of Dex on Apgar score and umbilical blood gas analysis [18-20]. In our study, 5ug of Dex as an adjuvant to bupivacaine did not affect Apgar score, and umbilical blood gas analysis showed no significant difference in pH, PO₂, PCO₂ and SO₂ between the two groups. The possible reason was that the dose of Dex was very small and it acted directly on the $\alpha 2$ -adrenoceptor in the spinal cord in this study.

Chill is a common complication of CSEA,

factors such as increased metabolic rate and blood circulation in the third trimester of pregnancy, compensatory vasoconstriction in the unobstructed area caused by hypotension after anesthesia, and increased heat dissipation after fetal dissection increase the incidence of chill. One study showed that 57% of women who underwent cesarean section under intraspinal anesthesia developed chill [21]. We found that intrathecal injection of Dex significantly reduced the incidence of chills. This is because Dex can inhibit Ca²⁺ influx in nerve endings, and decreases the postsynaptic membrane excitability, thereby lower the threshold of chills, and reducing vasoconstriction, preventing chills, and reducing the incidence of postoperative agitation [22, 23].

Umbilical artery pH at birth is frequently used as an index to measure perinatal acidaemia and assess birth asphyxia, low umbilical artery pH has been associated with obstetric complications and adverse neonatal outcomes, hypoxic-ischaemic encephalopathy, neonatal encephalopathy with seizures and neonatal mortality [24, 25]. In the current study, the pH value of umbilical artery between two groups shows no significant difference. Evidence shows that lactate is direct and more predictive measurement than pH or at least of equal importance [26, 27], and umbilical lactate is significantly corrected with MRS-measured brain lactate [28]. Lactate in the fetus is produced at the rate of 0.8mmol.Kg⁻¹.h⁻¹ under normal circumstances, but it will increase in response to stress, asphyxia, respiratory or circulatory failure. This study showed that the umbilical artery lactate of group D were significantly lower than group C, its mechanism needs further study.

The author found that compared with group C, group D had lower VAS score at

time T4, none of the parturient requested analgesic during the surgery. The mechanism by which intrathecal Dex enhance the sensory and motor block of local anesthetics is not well known. One possible reason is that Dex bind to pre-synaptic C-fibers and post-synaptic dorsal horn neurons, Dex produce analgesia by suppression the release of C-fiber transmitters and hyperpolarization of post-synaptic dorsal horn neurons [29, 30], this ant nociceptive effect may explain the prolongation of the sensory block when added to spinal anesthetics.

A series of clinical studies have shown that intravenous Dex can reduce stress response [31-32] and decrease the perioperative serum level of cortisol, EPI and NA [33]. In our study, there is a significant reduction in serum concentrations of EPI and NA in group D.

Khasawinah et al. believed that Dex could be effectively applied in the prevention and treatment of nausea and vomiting [34], but there was no significant difference in the rate of nausea and vomiting in Poupak R's study³⁵. Up to now, most clinical trials focus on the effect of intravenous Dex on nausea and vomiting. In this study, the incidence of nausea and vomiting in group D was significantly lower than that in group C. Possible reasons are: Dex may act directly on the α_2 - adrenoceptor in the vomiting center; And Dex can also reduce the sympathetic tension and the release of catecholamines, thus reducing the incidence of nausea and vomiting cause by high concentrations of catecholamines.

The most frequently reported adverse reaction to Dex were hypotension and bradycardia. A meta-analysis of several randomized controlled trials of Dex found the incidence of hypotension and bradycardia was significantly increased³⁶. Feng Xia et.al report that the incidence of hypotension in the Dex group was slightly lower than that in the control group [14]. We found that adding intrathecal dexmedetomidine as an adjuvant to hyperbaric bupivacaine for elective cesarean section did not affect parturients' hemodynamics.

Conclusion:

Adding intrathecal Dex as an adjuvant to hyperbaric bupivacaine for elective cesarean section can enhance the analgesic effect of bupivacaine, inhibit maternal stress response and reduce the incidence of nausea, vomit, chill, and the Apgar score of the newborns will not be affected.

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