Comparison of Intrathecal Dexmedetomidine and Fentanyl as Adjuvants to Levobupivacaine in Parturients Undergoing Elective Cesarean Sections

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Abstract

Background: The aim of this study was to evaluate the onset, duration of sensory and motor block, duration and quality of post-operative analgesia, and adverse effects of dexmedetomidine or fentanyl given intrathecally levobupivacaine in patients undergoing elective caesarean sections.

Methods: After approval of College Ethical Committee, 50 parturient with American Society of Anesthesiologists I-II undergoing elective cesarean section were enrolled for study with their informed consent. They were divided to two Groups each parturient received intrathecal levopubivacaine plus fentanyl or dexmedetomidine.

Results: Spinal anesthesia is the most commonly used regional technique for cesarean section. The addition of various additives may allow the dose of local anesthetic to be reduced.

Conclusion: Both regimen were effective in providing surgical anesthesia and hemodynamic stability, but levobupivacaine + fentanyl group offered an advantage of rapid onset of sensory and motor block and prolonged duration of sensory block and post-operative analgesia.

Key Words: Dexmedetomidine – Spinal anesthesia – Analgesia – Cesarean section.

Introduction

REGIONAL anesthesia is a safe, inexpensive technique, with advantage of prolonged post-operative pain relief which blunts autonomic, somatic, and endocrine responses [1].

Neuraxial anesthesia (spinal, epidural, and caudal) greatly expands the anesthesiologists' armamentarium, providing alternatives to general anesthesia when appropriate. Neuraxial blockade may reduce the incidence of venous thrombosis, pulmonary embolism, and cardiac complications in high-risk patients, bleeding, transfusion requirements, pneumonia and respiratory depression [2].

Spinal anesthesia is commonly used for the cesarean section, this is because of being an easily executed technique, with fast onset and favorable predicted outcome. It also allows the avoidance of the risks of general anesthesia and makes parturient to remain awake to enjoy the birthing experience [3].

Many additives has been proved to improve the quality of spinal anesthesia as opiods (morphine, fentanyl, and sufentanil) and other drugs such as epinephrine, clonidine, neostigmine, adenosine, midazolam, and magnesium sulfate [4].

For example, the addition of opioids to local anesthetics has been observed to improve the quality of analgesia, and reduce local anesthetic requirement, density of motor blockade and the incidence of instrumental deliveries while clonidine has also been combined successfully with local anesthetics for labour epidural analgesia [5].

Patients and Methods

After obtaining the ethics committee approval and written informed consent from the patients, 50 parturients (with the following inclusion and exclusion criteria) who are scheduled for elective caesarean section under spinal anesthesia in El-Kasr Al-Aini Teaching Hospital in period from July 2014 till September 2015 were enrolled in the study. All patients fulfilled the following inclusion criteria; age between 18-40 years old, ASA status I, II, body mass index below 35kg/m^2, gestational age ≥37 week, single tone pregnancy. While presence of any one of the following criteria excludes
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the parturients from the study; age below <18 years old and >40 year old, ASA physical status > II, body mass index above 35kg/m², urgent or emergency CS, hypertensive disorders of pregnancy (eg, pre-eclampsia and eclampsia), known allergy to local anaesthesia or opioids, general contraindications to regional anesthesia, cardiac, endocrinial, hepatic and renal diseases.

On arrival to the OR, Ringer’s lactate solution 500mL was administered for prophylactic volume preload before induction of anesthesia. Base-line Heart Rate (HR), Mean Arterial Pressure (MAP) and oxygen saturation (SpO₂) were recorded.

Parturients were randomly allocated into 2 groups using closed opaque envelope randomization, each parturient received intrathecal 2.5ml in form of 2ml 0.5% levobupivacaine (chirocaine amp by Abbott) completed to 2.5ml as follow:
- Group F; with 0.5ml fentanyl (25 µg) Fentanyl group.
- Group D; with 0.5ml 10% dexmedtomidine (5 µg) dexmedetomidine group.

Assessment of HR, MAP, SpO₂:

Independent anesthesiologist who was blinded to the injected drug recorded the following parameters, HR, MAP and SpO₂ immediately after intrathecal injection and every 3min from the 1st min to the 30th min then every 10min till the end of surgery, and every 20 minutes till discharge from the Post Anesthesia Care Unit (PACU). If maternal hypotension, defined as a more than 20% decrease in the base-line MAP occurred, it was promptly treated with repeated doses of ephedrine 3mg IV every 3min. and IV fluid (500ml of Ringer Lactate.) loading till blood pressure returns to its base line values. Bradycardia, defined as a heart rate <60 beats/min was treated with repeated dosed of atropine 0.5mg IV with maximum dose of 2mg. Duration of delivery which is defined as time interval from skin incision till delivery of baby and duration of surgery which is time from skin incision till skin closure was recorded in minutes.

Sensory and motor assessment:

Sensory block was assessed bilaterally at mid-clavicular line by pin-prick test, the following was recorded:
- Level of maximum sensory block.
- Sensory block time which is the time interval from intrathecal injection till the time sensory level reaches T10.
- Maximum sensory block time which is the time interval from intrathecal injection till the time of achieving maximum sensory level.
- Duration of sensory block which is defined as time interval from intrathecal injection till sensory level regresses to T10.

The assessment of motor block will be through measuring the following:
- The degree of motor block was determined according to the Bromage scale.
- The onset of motor block which is the time interval from intrathecal injection to Bromage score of 1.
- Duration of motor block is defined as time interval from intrathecal injection till the Bromage score returns to zero.

Sensory and motor block assessments were performed every minute until delivery, and subsequently at 5-min intervals until complete recovery of motor function was determined.

Visual analogue scale (VAS, 0 mm=no pain, 100mm=worst imaginable pain) was used to measure duration of complete (VAS=0) and effective (VAS <40/100mm) analgesia at 20-min intervals. Rescue analgesia was given in form of ketorolac 30mg IM if VAS >40 or on maternal request. Sedation was assessed using Ramsay sedation score on arrival to PACU, and then every 30min for 2 hours (Table 1).

Table (1): Ramsay sedation score.

<table>
<thead>
<tr>
<th>Score</th>
<th>Observation</th>
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<tbody>
<tr>
<td>1</td>
<td>• Anxious, agitated or restless.</td>
</tr>
<tr>
<td>2</td>
<td>• Cooperative, oriented and tranquil.</td>
</tr>
<tr>
<td>3</td>
<td>• Responsive to commands.</td>
</tr>
<tr>
<td>4</td>
<td>• Asleep, but with brisk response to light glabellar tap or loud auditory stimulus.</td>
</tr>
<tr>
<td>5</td>
<td>• Asleep, sluggish response to glabellar tap or auditory stimulus.</td>
</tr>
<tr>
<td>6</td>
<td>• Asleep, no response.</td>
</tr>
</tbody>
</table>

Statistical methods and sample size:

To detect a clinical significance difference of 30% for motor blockade recovery time between the 2 groups with power of 80% and alpha error of 5%, the sample size calculated is 48 patients are required (24/group) which will be increased to 50 patients (25/group) for possible drop outs.

Data were coded and entered using the statistical package SPSS Version 22. Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical
variables. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test. For comparing categorical data; Chi square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5.

*p*-values less than 0.05 were considered as statistically significant.

**Results**

In the present study, the anesthetic effects of levobupivacaine + fentanyl (F) and levobupivacaine + dexmedetomidine (D) were compared in a 50 patients who were scheduled for elective caesarean section under spinal.

Four patients were excluded at the beginning of our study due to technical difficulties in spinal anesthesia, converted to general anesthesia from the start. 50 parturient completed the study.

**Demographic data, duration of surgery:**

There were no statistically significant differences in terms of demographic data. Statistically insignificant differences (p<0.05) were observed regarding times from intrathecal injection to skin incision and skin to uterine incision. Total duration of surgery did not differ significantly between groups (Table 2).

**Sensory and motor block characteristics:**

There were no statistically significant differences between the two groups regarding the level of maximum motor block (Table 3). The time needed to reach the maximum motor and sensory block was significantly longer in D-group when compared to the other group. The duration of motor block in both F-group (332.4±86.09min) and D-group (265.42±44.33min) was comparable. Values are presented as mean ± SD.

**Hemodynamic parameters:**

Hypotension occurred at various time points (immediately after the intrathecal injection (73.6 ± 4.3) in F-group and (73.65±6.6) in D-group and after delivery of both fetus and placenta 20IU of oxytocin added to 500ml of intravenous fluid (68.35±4.43) in F-group and (72.7±5.03) in D-group. Throughout the study period in each group. There were no statistically significant differences (p<0.05) in IV vasopressor or atropine requirements. The heart rate showed a decrease from the base line after intrathecal block but this drop was not significant compared to baseline values and no bradycardia was observed.
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Fig. (1): Heart rate throughout the procedure.

Fig. (2): Mean arterial pressure throughout the procedure.

Adverse effects:

Nausea, vomiting, pruritus and the request of antiemetic therapy were comparable in all groups. Regardless of the drugs used for spinal anaesthesia, slight to moderate backache was observed in 3 of 49 parturients (Table 5).

Table (5): Adverse effect. Data presented as numbers and percentage.

<table>
<thead>
<tr>
<th></th>
<th>Levobupivacaine plus fentanyl (25ug) (n=25)</th>
<th>Levobupivacaine plus dexmedetomidine (5ug) (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>0 (0%)</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Shivering</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Backache</td>
<td>1 (4%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Postdural puncture headache</td>
<td>2 (8%)</td>
<td>3 (12.5%)</td>
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</table>

Sedation and post-operative analgesic requirement:

Sedation was assessed using Ramsay sedation score on arrival to PACU, and then every 30min for 2 hours and there were no difference among groups. Sedation score was 1 in all patients in all four groups according to Ramsay's sedation score.

The post-operative ketorolac 30mg IM (ketolac amp.of amriya pharm.) requirements after 6 hours (Table 6) were 12 in the F-group and 14 in the D-group. The 6-to 24-h requirements for non opioid analgesics did not differ significantly among the two groups.

Table (6): Analgesic requirement after 6 hours. Data presented in numbers and percentage.

<table>
<thead>
<tr>
<th></th>
<th>Levobupivacaine plus fentanyl (25ug) (n=25)</th>
<th>Levobupivacaine plus dexmedetomidine (5ug) (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic require 6hr</td>
<td>12 (48%)</td>
<td>14 (58.3%)</td>
</tr>
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</table>

Discussion

This study revealed that in full term parturients undergoing elective Cesearean section under spinal anesthesia the addition of fentanyl 25 g.g to levobupivacaine 10mg improves the sensory and motor block characteristics, prolongs post-operative analgesia with decreased requirement of rescue analgesics in the post-operative period, without increasing the incidence of side effect and complications.

Intrathecal Dexmedetomidine 5 g.g with Levobupivacaine 10mg is a safe combination for spinal anesthesia and provides longer sensory and motor blockade for longer surgeries and provides a good post-operative analgesia without producing significant adverse reactions.

Our results are generally in line with the findings of previously published relevant experimental and clinical trials [6,7].

Akan et al., while using 10mg plain levobupivacaine and comparing it with 7.5mg levobupivacaine plus 25 g.g fentanyl and 7.5mg levobupivacaine plus 2.5g sufentanil in patients undergoing transurethral resection of the prostate under spinal anaesthesia concluded that combining lower doses of levobupivacaine with fentanyl and sufentanil provides faster onset of sensory block, lower frequency and shorter duration of motor block and prolonged analgesia time [8].

Cuvas et al., [9] also added 15 g.g fentanyl to lower dose of levobupivacaine 2.3ml and compared it with 2.5ml of plain levobupivacaine. The time to onset of sensory and motor block, regression of sensory block to S 1 was similar in both groups.
Duration of motor block was shorter in fentanyl group. Levobupivacaine used was less in this group. Addition of fentanyl to levobupivacaine resulted in higher sensory level (T6) as compared to plain levobupivacaine (T9). The difference in the level of sensory block in both the groups can be explained by the difference in the baricity of the injected solutions. Opioids are hypobaric and when added to hypobaric LA will make the mixture more hypobaric thus altering the density of resulting solution which effects the direction and extent of spread in spinal block. Girgin et al., while using 5mg levobupivacaine plus 25\(\mu\)g fentanyl and 7.5mg levobupivacaine plain demonstrated that maximum sensory level was T7 and T6 respectively; however the maximum motor block achieved was Bromage 2 in both groups. In this study maximum sensory level achieved was lower in combination group which might be due to the low dose of levobupivacaine used in this group [10].

In a study by Bremerich et al., involving 60 patients who were scheduled for caesarean section and were administered 0.5% levobupivacaine (10 mg) and 0.5% bupivacaine (10mg) in combination with opioid (10 and 20\(\gamma\)g of fentanyl and 5\(\gamma\)g of sufentanil), the duration of motor block was found to be shorter with levobupivacaine compared to bupivacaine. The number of patients with Bromage score 3 block was 5 in the levobupivacaine group (n=30) and 21 in the bupivacaine group (n=30) [11].

In our study, the onset of the sensory block was in dexmedetomidine group (3.9min) and Fentanyl group (3.22min), and time to Bromage 3 was (4.44 min) in D-group and (3.74min) in F-group.

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective \(\alpha\)2-adrenoceptor agonism. Activation of the receptors in the brain and spinal cord inhibits neuronal firing and results in sympathlytic effect, causing hypotension, bradycardia, sedation, and analgesia [12]. Dexmedetomidine exerts its analgesic effects via binding to \(\alpha\)2-adrenergceptors in the spinal cord [13] Alpha 2 agonists act by additive or synergistic effect secondary to different mechanisms of action from local anesthetics. Local anaesthetics act by blocking sodium channels. Alpha 2 adrenoceptor agonists act by binding to pre synaptic C-fibers postsynaptic dorsal horn neurons. Intrathecal Dexmedetomidine is 8 times more specific and highly selective alpha 2 adrenoceptor agonist compared to Clonidine, thereby making it a useful and safe adjunct [14].

Dexmedetomidine have been used in many studies intrathecally with no adverse neurotoxicity or neurologic deficits [15]. Dexmedetomidine is a better neuraxial adjuvant to Ropivacaine when compared to Clonidine for providing early onset and prolonged post-operative analgesia and stable cardio respiratory parameters [16].

Kanazi et al., used a small intrathecal dose of dexmedetomidine (3\(\gamma\)g), in combination with bupivacaine on humans for spinal anesthesia. Results showed a shorter onset of motor block and a prolongation in the duration of motor and sensory block with hemodynamic stability and lack of sedation [16].

Ogan et al., showed an earlier significant peak sensory block in the Intrathecal Bupivacaine & dexmedetomidine group compared to the Bupivacaine with Fentanyl groups [14].

Shukla et al., also showed that the onset time to reach peak sensory level was shorter in dexmedetomidine group as compared with the control group using bupivacaine alone [17].

In a study by Gupta et al., dexmedetomidine added to intrathecal ropivacaine led to a prolongation in the motor and sensory block durations [18]. In another study by Gupta et al., demonstrated that intrathecal dexmedetomidine prolonged the duration of motor and sensory blockade with hemodynamic stability and the duration of motor and sensory block; when compared with fentanyl, it reduced the analgesic requirement in 24h [19].

The results of Vania Kanvee et al., study that compare the analgesic efficacy and block characteristics among two alpha 2 agonists with local anesthetic Levobupivacaine clearly indicate that intrathecal Dexmedetomidine significantly prolongs duration of sensory and motor block and duration of spinal anesthesia in comparison to Clonidine. Vania Kanvee et al., study shows that there is no difference in time of onset of sensory and motor block between intrathecal Clonidine and [20].

Maroof et al., used dexmedetomidine epidurally at approximately 1.5\(\gamma\)g/kg to decrease the incidence of post-operative shivering without any reports of neurological deficit [21].

Yekta and Belli studied the effects of 2\(\gamma\)g and 4\(\gamma\)g doses of dexmedetomidine in combination with intrathecal hyperbaric bupivacaine on spinal anesthesia and its post-operative analgesic characteristics and found that 4\(\gamma\)g dose of dexmedetomidine, an intrathecal adjuvant, leads to hemodynamic
stability and remarkable effects on spinal anesthesia, and can be safely used to decrease analgesic requirement in the post-operative period with intrathecal hyperbaric bupivacaine because it significantly prolongs the sensory and motor block duration [17].

In this study, Transient hypotension occurred at various time points i.e immediately after intrathecal injection and after intravenous infusion of oxytocine after delivery of baby throughout the study period in each group. There were no statistically significant differences in IV vasopressor or atropine requirements. The heart rate showed a decrease from the base line after intrathecal block but this drop was not significant compared to baseline values and no bradycardia was observed.

Gunusen et al., compared different doses of intrathecal levobupivacaine combined with fentanyl and they observed that the incidence of hypotension was higher in the levobupivacaine 10mg group, although this group provided more effective anesthesia and greater patient and surgeon satisfaction with spinal anesthesia compared with the other two groups. Levobupivacaine 5mg plus fentanyl 25 µg remained inadequate for cesarean section under spinal anesthesia owing to the higher epidural dose required. Levobupivacaine 7.5mg plus fentanyl 15 µg was found to be suitable due to the lower incidence of hypotension than when levobupivacaine 10mg plus fentanyl 10 µg was used, and the reduced need for epidural supplementation when levobupivacaine 5mg plus fentanyl 25 µg was employed [22].

In Turkmen et al., study, hypotension was noted in 13 patients in Bupivacaine + Fentanyl group and in 9 patients in Levobupivacaine + Fentanyl group. No statistically significant difference was observed between the groups with respect to MAP [23]. In Girgin et al., study, heart rate and blood pressure remained stable and comparable in the fentanyl group and control group of plain levobupivacaine intraoperatively as well as postoperatively [24].

Chattopadhyay et al., concluded that addition of fentanyl to levobupivacaine does not increase the incidence of bradycardia [25].

Lee et al., also concluded that there was no significant difference in the mean heart and blood pressure in plain levobupivacaine group and levobupivacaine plus fentanyl group [26].

Ashraf AM et al., studied Efficacy of Intrathecally Administered Dexmedetomidine versus Dexmedetomidine with Fentanyl and regarding hemodynamic variables measured during the intraoperative period, they found that there was a significant reduction in pulse rate starting at 20 minutes until 120 minutes in the dexmedetomidine + group and starting at 20 minutes until 60 minutes in the dexmedetomidine group in comparison to the control group. Systolic blood pressure showed a significant reduction starting at 5 minutes until 90 minutes intraoperatively in both the dexmedetomidine and dexmedetomidine + groups in comparison to the control group. There was a significant reduction in intraoperative diastolic blood pressure starting at 5 minutes until 20 minutes intraoperatively in both the dexmedetomidine and dexmedetomidine + groups in comparison to the control group. There were no significant differences between groups in hemodynamic variables measured during the post-operative period [27].

In this study sedation score was 1 in all patients in all groups according to Ramsay's sedation score. Even addition of dexmedetomidine (5 µg) doesn't cause sedation. Administration of an a2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation. In Yekta’s study, 40% of the patients in the 4 µg dexmedetomidine group developed sedation in the range of RSS = 2 to 4 [13].

Spinal anesthesia is not a 100% certain successful technique. Failure rates of 0.72% to 16.0% have been reported [28].

In our study there was a percentage of failed spinal, in control group 3 patient with percentage of 12%, F-group there was no failure, M-group 2 cases with percentage of 8% and D-group one case with percentage of 4%.

According to Pokharel A [29], technical errors are common causes of failed spinal anesthesia like: Drug deposition at lower spinal level than surgical site, improper rate of injection, failure to recognize dural puncture, needle partly inside/outside dural sac, patient co-operation, needle in ventral epidural space and lateral horizontal position (25%).

Chemical interactions are also contributory like: Bloody tap causes hydrolysis of ester type anesthetics by pseudo-cholinesterase, concentration errors, loss of potency by prolonged exposure to light, high CSF pH, glucose causes hyperalgesia and spotty anesthesia [30].
Horlocker and Wedel Human reported the density of many local anesthetics adjusted for temperature to match human normal temperature \[31\]. Increasing the drug temperature from room temperature to 37 degrees centigrade decreases the drug's density. Human Cerebrospinal Fluid (CSF) has a specific gravity of 1.00063 to 1.00075 at 37 degree centigrade generally, and 1.00030 gram per milliliter in term pregnant woman \[32,33\].

In the training environment the incidence of failed spinal anesthesia can be as high as 25% or 1 in 6 \[30\].

**Conclusion:**

After considering all these factors, we can conclude that adding fentanyl 25 \(\mu g\) or dexmedetomidine 5 \(\mu g\) to levobupivacainein 10mg spinal anesthesia for elective cesarean section result in shortening time to sensory and motor block in the levobupivacaine + fentanyl group and levobupivacaine + dexmedetomidine also a prolongation of duration of analgesia and decrease in postoperative analgesia requirement.

Fentanyl and dexmedetomidine in the doses used in this study are safe adjuvants with hemodynamic stability.

**References**


