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

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Abstract

Background: 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, producing a synergistic effect. The aim of this study was to investigate the block characteristics of using different additives to intrathecal levobupivacaine.

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 randomly divided equally to two Groups each parturient received intrathecal 2.5ml in form of 2ml 0.5% levopubivacaine completed to 2.5ml as follow: With 0.5ml fentanyl (25 µg) Fentanyl group (group-F) and with 0.5ml 10% MgSO₄ (50mg) Magnesium sulphate group (group-M).

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, producing a synergistic effect that is more prolonged in levobupivacaine and fentanyl group as compared to levobupivacaine and magnesium group.

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 postoperative analgesia.

Key Words: Magnesium – Levobupivacaine – Spinal anesthesia – Analgesia – Cesarean section.

Introduction

REGIONAL anesthesia is a safe, inexpensive technique, with advantage of prolonged postoperative 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. They may also be used simultaneously with general anesthesia or afterward for postoperative analgesia and for the management of acute and chronic pain disorders. When neuraxial blockade is used either alone or in combination with general anesthesia it may reduce the incidence of venous thrombosis, pulmonary embolism, 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 opioids (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,
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52 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 the parturients from the study: age below <18 years old and >40 year old, ASA physical status $\geq$ III, body mass index above 35kg/m$^2$, urgent or emergency CS, hypertensive disorders of pregnancy (e.g, pre-eclampsia and eclampsia), known allergy to local anaesthesia or opioids, general contraindications to regional anesthesia, cardiac, endocrinal, 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 (SpO$_2$) 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% levopubivacaine (chirocaine amp by Abbott) completed to 2.5ml as follow:

- Group A; with 0.5ml fentanyl (25 $\mu$g) Fentanyl group.

- Group B; with 0.5ml 10% MgSO$_4$ (50mg) Magnesium sulphate group.

### Assessment of HR, MAP, SpO$_2$

Independent anesthesiologist who was blinded to the injected drug recorded the following parameters, HR, MAP and SpO$_2$ immediately after intrathecal injection and every 3min from the 1$^{st}$ min to the 30$^{th}$ 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). 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 T 10.

- 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, 0mm=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. |
|-------------------|-----------------|
| Score | Observation |
| 1 | • Anxious, agitated or restless. |
| 2 | • Cooperative, oriented and tranquil. |
| 3 | • Responsive to commands. |
| 4 | • Asleep, but with brisk response to light glabellar tap or loud auditory stimulus. |
| 5 | • Asleep, sluggish response to glabellar tap or auditory Stimulus. |
| 6 | • Asleep, no response. |
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 ($\chi^2$) 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), levobupivcane + magnisum (M), 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. One hundred parturient completed the study.

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.

Data collected showed failure of spinal anesthesia in 2 cases among the 50 cases. There was 2 cases were complete failure with no effects. Those patients received general anesthesia and were excluded from our study.

Sensory and motor block characteristics:
There were no statistically significant differences between the two groups regarding the level of maximum motor block (Table 2). The time needed to reach the maximum motor and sensory block was significantly shorter in F-group ($4.66 \pm 0.76$min), ($4.02 \pm 0.81$min) respectively when compared to the Magnesium group ($6.73 \pm 1.66$min) while the duration of motor and sensory block were significantly longer in F-group ($332.4 \pm 86.09$min) ($398 \pm 75.55$min) respectively than M group ($178.26 \pm 37.34$min) ($260.43 \pm 54.33$min). The time needed to reach the maximum motor and sensory block was significantly longer in M-group when compared to the F-group. While the duration of motor and sensory block were significantly shorter in M-group when compared to the F-group.

<table>
<thead>
<tr>
<th>Level of maximum sensory block:</th>
<th>F-group (n=25)</th>
<th>M-group (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>20 80.0</td>
<td>17 73.9</td>
<td>0.025</td>
</tr>
<tr>
<td>T6</td>
<td>5 20.0</td>
<td>6 26.1</td>
<td></td>
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<tr>
<td>T10</td>
<td>0 0</td>
<td>0 0</td>
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$p$-values less than 0.05 were considered as statistically significant.

Hemodynamic parameters:
Hypotension occurred at various time points (immediately after the intrathecal injection ($73.6 \pm 4.3$) in F-group, ($73.54 \pm 5.13$) in M-group and after delivery of both fetus and placenta 20IU of oxytocin added to 500ml of intravenous fluid ($68.35 \pm 4.43$) in F-group and ($72.5 \pm 6.53$) in M-group.

Throughout the study period in each group (Table 4). There were no statistically significant differences ($p>0.05$) in IV vasopressor or atropine
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Sedation and post-operative analgesic requirement:

Sedation was assessed using Ramsay sedation score (88) on arrival to PACU, and then every 30min for 2 hours and there were no difference among the two groups. Sedation score was 1 in all patients in all two groups according to Ramsay's sedation score.

The postoperative ketorolac 30mg IM (ketolac amp. of Amriya pharm.) requirements after 6 hours (Table 5) were 12 in the F-group and 18 in the M-group. The 6-to 24-h requirements for non opioid analgesics did not differ significantly among the groups.

Table (5): Analgesic requirement after 6 hours. Data presented in numbers and percentage.

<table>
<thead>
<tr>
<th></th>
<th>Levobupivacane</th>
<th>Levobupivacane</th>
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<tr>
<td></td>
<td>plus fentanyl</td>
<td>plus magnesium</td>
</tr>
<tr>
<td></td>
<td>(25ug) (n=25)</td>
<td>(75mg) (n=23)</td>
</tr>
<tr>
<td>Analgesic requirement 6hr</td>
<td>12 (48%)</td>
<td>18 (78%)</td>
</tr>
</tbody>
</table>

Discussion

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

However, the addition of MgSO₄ 75mg levobupivacaine 10mg led to significant delay in onset of both motor and sensory blockade and delay in time needed to reach maximum sensory and motor block. The duration of both sensory and motor blockade was shorter compared to Fentanyl 25 µg.

Our results are generally in line with the findings of previously published relevant experimental and clinical trials [6-9].

In the present study, time to onset of sensory block and the time to achieve maximum sensory and motor block were more rapid, the duration of sensory and motor block and postoperative analgesia was more prolonged in levobupivacaine and fentanyl group as compared to mgsO₄ levobupivacaine group. Requirement of postoperative rescue analgesics was less in F-group.
Ozyilkan et al., compared 2.2ml of levobupivacaine plain with 10 µg fentanyl or 2.5 µg sufentanil as adjuvant in spinal anesthesia for caesarean section. They found that the onset of sensory and motor block was achieved more rapidly in fentanyl and sufentanil group. Duration of sensory and motor block and time for first analgesic requirement was longer in adjuvant groups as compared to plain group [10].

They concluded that adding an opioid to the local anesthetic may confer a local anesthetic-sparing effect and lead to a shorter onset time for sensory block and a prolongation of the duration of the sensory block without affecting the motor block, reducing the incidence of intraoperative pain. The opioid interrupts pain transmission in the dorsal horn while the local anesthetic blocks conduction in the motor and sensory nerves [10,11].

Akan et al., while using 10mg plain levobupivacaine and comparing it with 7.5mg levobupivacaine plus 25 µg fentanyl and 7.5mg levobupivacaine plus 2.5 µg 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 [12].

However in the present study, motor block duration was prolonged in group F-group as compared to magnesium group. This difference might be due to the use of equal doses of levobupivacaine in both groups. Cuvas et al., [13] also added 15 µg of 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 µg 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 [14].

In a study by Bremerich et al., involving 60 patients who were scheduled for caesarean section and were administered 0.5% levobupivacaine (10mg) in combination with opioid (10 and 20 µg of fentanyl and 5 µg 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) [15].

In our study, the onset of the sensory block was earlier in Fentanyl group (3.22min), compared magnesium group (5.12min) and time to Bromage 3 was significantly less in F-group (3.74min) than M-group (5.37min). As regards the first time to require analgesia, and total analgesic consumption in 24 hours, M-group (78%) showed a significant increase in time to first analgesic dose compared to control group, and significant decrease in the total analgesic consumption without any sedation.

In our study, adding magnesium sulphate 75mg to levobupivacaine didn’t shorten the onset of time of sensory (5.12 ± 1.31min) and motor block (5.7 ± 1.17min), the duration of sensory and motor block where shorter in magnesium group while the time to reach maximum level of sensory block was slower in this group (5.9min).

The parturient received 25 µg of fentanyl significantly prolonged the duration of anesthesia (398±75min.) compared with magnesium 75mg (260.4±54.3min).

The NMDA receptor channel complex contains binding sites for noncompetitive antagonists such as magnesium, activation of C-fibers leads to neuronal excitation, which is diminished by NMDA receptor antagonists, hence the use of magnesium as an adjuvant for intrathecal block [16]. It acts as an antagonist at NMDA receptor: NMDA receptor antagonist can prevent central sensitization due to peripheral nociceptive stimulation and can abolish such hypersensitivity once it is established [17].

It is difficult to understand why magnesium should have less effect than fentanyl. It is either possible that magnesium is removed from extra-
cellular fluid rapidly or that the ion is specific to the NMDA receptor channel and does not influence the opioid receptor sites to which the opioid binds [18].

Mitra Jabalameli and Seyed Hamid Pakzadmoghadam evaluated different intrathecal doses of magnesium sulfate in parturients undergoing the elective caesarean section and they found that the addition of 50, 75, or 100mg magnesium sulfate 50% to hyperbaric bupivacaine spinal anesthesia led to a significant delay in the onset of both sensory and motor blockade, and prolonged the duration of sensory and motor blockade without increasing major side effects. The median duration of sensory and motor blockade might result in increasing some of side effects (hypotention, nausea, and vomiting [19].

H. Unlugenc et al., find that the patient undergoing cesarean section with spinal anesthesia, the addition of MgSO\textsubscript{4} (50mg) intrathecal to 10mg of bupivacaine (0.5%) did not shorten the onset time of sensory and motor blockade or prolong the duration of spinal anesthesia as seen with fentanyl [20].

Buvanendran et al., studied the dose of magnesium in which 50mg of intrathecal MgSO\textsubscript{4} potentiated fentanyl antinociception [21].

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 vasoressor 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 was remained inadequate for cesarean section under spinal anesthesia owing to the higher epidural dose required. Levobupivacaine 7.5mg plus fentanyl 15 was found to be suitable due to the lower incidence of hypotension than when levobupivacaine 10mg plus fentanyl 10 was used, and the reduced need for epidural supplementation than when levobupivacaine 5mg plus fentanyl 25 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 [23].

Chattopadhyay et al., concluded that addition of fentanyl to levobupivacaine does not increase the incidence of bradycardia [14].

Akan 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 [12]. Similar results were reported by Cuvas et al., [13] and Lee et al. [24].

Spinal anesthesia is not a 100% certain successful technique. Failure rates of 0.72% to 16.0% have been reported [25].

In our study there was a percentage of failed spinal, F-group there was no failure, M-group 2 cases with percentage of 8%.

According to Pokharel [26], Technical errors are common causes of failed spinals 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 [27].

Horlocker and Wedel Human reported the density of many local anesthetics adjusted for temperature to match human normal temperature [28]. 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 degrees centigrade generally, and 1.00030 gram per milliliter in term pregnant woman [29].

In the training environment the incidence of failed spinal anesthesia can be as high as 25% or 1 in 6 [27].

Conclusion:

After considering all these factors, we can conclude that Adding fentanyl 25 µg to levobupivacaine 10mg spinal anesthesia for elective cesarean section result in shortening time to sensory and motor block and also a prolongation of duration of analgesia and decrease in postoperative analgesia requirement. While the addition of magnesium sulphate 75mg results in delay in onset of motor and sensory blockade.

Further studies should be conducted to study the benefits, advantage and disadvantage of levobupivacaine and adjuncts in anesthesia in preeclamptic patients.

References


3- MITRA JABALAMELI and SEYED HAMID PAKZADMOGHADAM: Adding different doses of magnesium sulphate for spinal anesthesia in cesarean section. Advanced biomedical Resarch, 1; 7, 2012.


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