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**KLİNİK ARAŞTIRMA** *Anesteziyoloji ve Reanimasyon*

# Comparison of intrathecal hyperbaric bupivacaine and levobupivacaine with fentanyl for caesarean section

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**SUMMARY**

***Background:*** *Use of levobupivacaine as pure S(-) enantiomer of bupivacaine is progressively increased due to lower cardiotoxicity and neurotoxicity and shorter motor block duration.. The aim was to compare the efficacy of lower dose local anesthetics use together with higher opioid dose to decrease side effects of drugs. We compared sensorial, motor block levels and side effects of equal doses of hyperbaric bupivacaine and levobupivacaine with intrathecal fentanyl addition in elective caesarean cases.*

***Methods:*** *After hospital ethics committee approval and getting written informed consent from patients, eighty patients with ASA I-II aged 18-45 were included in the study. They were randomized to either Group BF receiving 7.5 mg (1.5 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl, or Group LF receiving 7.5 mg (1.5 ml) hyperbaric levobupivacaine and 25 mcg (0.5 ml) fentanyl.*

***Results:*** *ASA II cases were higher in Group LF. Hemodynamic parameters such as 45th min mean arterial pressure of Group BF was found to be lower ($p<0.05$). Max. motor block level, motor block level, found to be higher in Group BF ($p<0.05$). In Group LF, max sensorial block level and postoperative VAS scores were higher ($p<0.05$). Arterial blood gas $PCO_2$ was higher and $PO_2$ was lower in Group BF ($p<0.05$). Onset of motor block time, time to max motor block, time to $T_4$ sensorial block, reversal of two dermatome, first analgesic need were similar in both groups.*

***Conclusion:*** *Intrathecal hyperbaric levobupivacaine-fentanyl combination is good alternative to bupivacaine-fentanyl combination in cesarean surgery as it is less effective in motor block, it maintains hemodynamic stability at higher sensorial block levels.*

***Key words:*** *Bupivacaine, levobupivacaine, fentanyl, spinal anesthesia, caesarean section*

**ÖZET**

**Sezaryende intratekal fentanil ilavesi ile birlikte hiperbarik bupivakain ve levobupivakainin karşılaştırılması**

***Amaç:*** *Bupivakainin saf S (-) enantiyomeri olan levobupivakainin kullanımı daha az kardiyotoksisite ve nörotoksisitesi ile daha kısa motor blok süresi olması nedeniyle giderek artmaktadır. Çalışmanın amacı, ilaçların yan etkileri azaltmak için daha yüksek opioid dozu ile birlikte düşük doz lokal anestezik-lerin etkinliğini karşılaştırmaktır. Elektif sezaryen olgularında intratekal fentanil ilavesi ile eşit dozlarda hiperbarik bupivakain ve levobupivakainin duyusal, motor blok seviyesi ve yan etkilerini karşılaştırdık.*

***Yöntem:*** *Hastane etik kurul onayı ve hastalardan yazılı bilgilendirilmiş onam alındıktan sonra 18-45 yaş, ASA I-II olan seksen hasta çalışmaya dahil edildi. Hastalar 7.5 mg (1.5 ml) hiperbarik bupivakain ve 25 mcg (0.5 mL) fentanil alan Grup BF ya da 7.5 mg (1,5 ml) hiperbarik levobupivakain ve 25 mcg (0.5 mL) fentanil alan Grup LF'ye randomize edildi.*

***Bulgular:*** *ASA II vakalar Grup LF'de daha fazlaydı. Grup BF'de 45. dk. ortalama arter basıncı gibi hemodinamik parametrelerinin daha düşük olduğu tespit edildi ($p<0.05$). Maks. motor blok seviyesi, motor blok seviyesi Grup BF'de daha yüksek bulundu ($p<0.05$). Grup LF'de, maksimum duyusal blok seviyesi ve postoperatif VAS skorları daha yüksekti ($p<0.05$). Grup BF'de arter kan gazı $PCO_2$ değeri yüksek ve $PO_2$ daha düşüktü ($p<0.05$). Motor blok başlama süresi, maksimum motor bloğa ulaşma süresi, $T_4$ duyusal bloğa ulaşma süresi, iki dermatomda gerileme ve ilk analjezi ihtiyacı her iki grupta da benzer bulundu.*

***Sonuç:*** *İntratekal hiperbarik levobupivakain-fentanil kombinasyonu sezaryenda daha az motor blok etkisi olması nedeniyle bupivakain-fentanil kombinasyonuna iyi bir alternatiftir, daha yüksek duyusal blok seviyelerinde hemodinamik stabilite sağlar.*

***Anahtar kelimeler:*** *Bupivakain, levobupivakainin, fentanil, spinal anestezi, sezaryen*

Spinal and epidural administration of local anesthetics during caesarean section produce analgesia, anesthesia and motor block, depending on the volume, concentration, and doses of drug used [1,2].

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For the local anesthetics selection, it is known that the agent's onset and duration of action, sensorial block level to motor block level and cardiac toxicity should be considered. 0.5 % heavy bupivacaine is more commonly used for spinal anesthesia for Caesarean section [3]. Levobupivacaine, being the S enantiomer of bupivacaine, is less cardiotoxic and less neurotoxic in cases of accidental intravascular injection and has shorter duration of motor block than racemic bupivacaine, its use increased progressively [4,5]. There is the clinical profile of potency for motor block for the pipecolylxlidines when administered spinally: low, intermediate, and high for ropivacaine, levobupivacaine, and bupivacaine, respectively [1,6].

The use of low doses anesthetics and opioids in spinal anesthesia were reported to have advantages such as faster onset of action, better efficacy with minimum toxic effect and selective sensorial block [4].

Fentanyl can be combined with local anesthetics for spinal anesthesia, and when used in this way it prolongs the duration of action and spread of sensory block as well [7]. Fentanyl has been combined with bupivacaine for lower limb surgery and also for inguinal herniorrhaphy and caesarean section [7-10].

We planned to compare the onset and duration of action, sensorial, motor block levels and side effects of equal doses of hyperbaric bupivacaine and levobupivacaine with intrathecal fentanyl addition in spinal technique in elective cesarean cases. Our aim was to compare the efficacy of low dose local anesthetics use together with higher opioid dose to decrease side effects of drugs.

## MATERIALS and METHODS

This prospective double-blinded randomized study is performed in between February and December 2009. The study was approved by institutional ethics committee and patients provided written informed consent before inclusion. The study was conducted in adherence with ICH/GCP and local regulations.

Total of eighty patients aged between 18-45 years, classified as ASA I-II and undergoing elective cesarean surgery were included in the study. Patients with history of allergy to any study drug, with any contraindication to regional anesthesia, pregnancy associated hypertension and placenta previa were not included in the study.

The injector with the drug was prepared by the study coordinator according to software which was carefully designed to prevent duplicate injections. The injectors were numbered and given to the staff who did not know the content. Also, patients did not know which agent they were given.

All patients were evaluated initially by medical history and a complete physical examination. No premedication was administered. After iv prehydration with 500 mL of 0.9 % isotonic NaCl infusion hemodynamic variables were monitored with ECG, systolic and diastolic blood pressure, cardiac heart rate and oxygen saturation ($SpO_2$). Mean arterial pressure (MAP) decrease of 30 % of MAP before block, accepted as hypotension. It was treated with 5 ml/kg fluid replacement and iv 5 mg ephedrine. Total ephedrine use was recorded.

All cases in sitting position were administered 3 ml (60 mg) 2 % lidocaine infiltration anesthesia through $L_{3-4}$ after disinfected with antiseptic solution. After infiltrating epidural space with "resistance loss" technique via 18 gauge Tuohy needle, intrathecal space is reached with 27 gauge spinal needle. They are randomized to either Group B receiving 7.5 mg (1.5 ml) hyperbaric bupivacaine (Marcaine®; Zentiva) and 25 mcg (0.5 ml) fentanyl, or Group L receiving 7.5 mg (1.5 ml) hyperbaric levobupivacaine (Chirocaine®, Abbott Laboratories) and 25 mcg (0.5 ml) fentanyl. After administration of drugs into intrathecal space, patients were placed in the supine position with left uterine displace-

ment and 10-150 elevation of the head of the bed. Surgery is started when sensorial block level reached $T_4$.

The hemodynamic parameters were monitored at 1st, 3rd and 5th min and recorded every 5 min until it had resolved. Sensorial-motor block was recorded at 1st, 3rd and 5th min and it was recorded every 15 min until reversal of motor block.

Pin-prick test is used for sensorial block evaluation. Highest dermatome level as maximum sensorial block level, time duration to $T_4$ dermatome block after drug administration, time duration to onset of $T_4$ sensorial block, sensorial block reversal time in two dermatome and time to first analgesic need were recorded as first analgesia time.

The most frequently used measure of motor block is the Bromage scale. In this scale, the intensity of motor block is assessed by the patient's ability to move their lower extremities (0=Free movement of legs and feet; 1=Just able to flex knees with free movement of feet; 2=Unable to flex knees, but with free movement of feet; 3=Unable to move legs or feet).

"Onset of motor block" is recorded as when Bromage scale is "1" after administration of local anesthetics, "onset of highest motor block" is recorded as time to reach highest scale of motor block, "motor block time" is recorded as time to complete termination of motor block, "maximum motor block level" is recorded as highest motor block scale that is reached.

"Duration of baby birth" is recorded as time to clamping of umbilical cord after administration of local anesthetics. "Operation duration" is recorded as time until end of operation after administration of local anesthetics.

Pain intensity was recorded during skin incision, uterus incision, and closure of periton, postoperative 30 min, and postoperative 60 min and when there is pain. In assessment of pain intensity, 10 cm visual analogue scale (VAS) is used. Before operation, VAS was explained to patients as; "0" no pain, "10" intolerable pain. During operation, in cases where analgesia was insufficient (VAS: 3-4), local anesthetics was applied and patients were excluded from the study in BF group.

Newborn 1 min and 5 min apgar scores and umbilical vein blood gases were recorded. Side effects such as pruritus, nausea, vomiting, anxiety, respiratory depression, and headache were followed.

Statistical analysis is performed by SPSS (Statistical Package For Social Sciences) for windows 17.0 program. All data were expressed as means, standard deviation, and frequency. Statistical significance was accepted as $p<0.05$. The comparisons between groups were tested using independent t-test. The comparisons within groups were tested using Fisher's Exact Test and chi-square test.

## RESULTS

### Demographical data of study population

Total of eighty patients were included in the study. However, in two patients, due to insufficient regional anesthesia, additional local anesthetics were given and patient was excluded from the study as the doses were changed.

No significant differences were detected among

**Table 1. Demographical data of study population.**

| | | Group LF Mean ± SD | Group BF Mean ± SD | P value |
|---|---|---|---|---|
| Age (year) | | 28.75±4.41 | 29.21±3.98 | 0.735 |
| Height (cm) | | 160.90±6.66 | 160.16±4.42 | 0.686 |
| Weight (kg) | | 76.40±11.09 | 74.74±9.98 | 0.626 |
| Gestational age (day) | | 270.95±8.64 | 271.74±6.33 | 0.749 |
| | | **n (%)** | **n (%)** | **P value** |
| ASA | I | 22 (55 %) | 8 (21 %) | 0.048* |
| | II | 18 (45 %) | 30 (79 %) | |

*Group LF: 7.5 mg (1.5 ml) hyperbaric levobupivacaine and 25 mcg (0.5 ml) fentanyl, Group BF: 7.5 mg (1.5 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl*

the groups with respect to age, weight, height, and gestational age. In Group BF, ASA II cases were higher ($p<0.05$), where there was no difference in Group LF (Table 1).

**Hemodynamic Parameters**

Basal heart rate of Group LF was 93.10±14.14 rate/min and 89.21±12.78 rate/min in Group BF. There was no significant difference between heart rate of groups both preoperatively and postoperatively ($p>0.05$).

Preoperative mean arterial pressure of Group LF was 94.20±14.33, and mean arterial pressure of Group BF was 91.68±09.27. There was significant difference between mean arterial pressure (MAP) of groups at 45th min ($p=0.017$). MAP of Group LF (86.30±08.80) was significantly higher than Group BF (79.32±08.90). At other time measurements, there was no difference between MAP of groups ($p>0.05$; Figure 1).

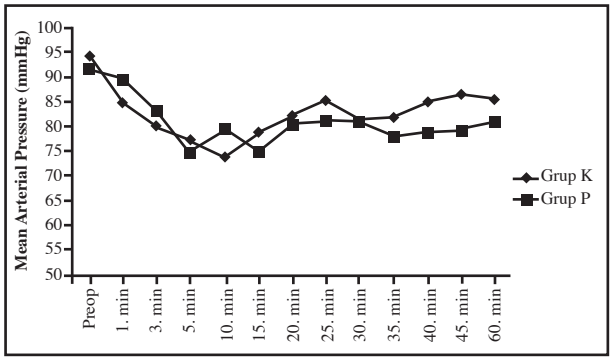


**Figure 1. Mean arterial pressure measurements of the groups.**

$SpO_2$ measurements were not different between groups ($p>0.05$).

**Visual Analogue Scale**

Postoperative VAS was found to be higher in Levobupivacaine group (Group LF; $p<0.05$). VAS of "skin incision" and "uterus incision" of all individuals in both groups were recorded as "0". There was no significant difference between "periton closure" VAS scores of groups. However postoperative 30th min and 60th min VAS distribution of groups were significantly different between groups ($p<0.05$; Figure 2). In Group BF, VAS with "0" was in 84 % of patients at postoperative 30th min measurement, in Group LF, VAS with "0" was in 41 % of patients, VAS was predominantly "0" (42 %) and "1" (37 %) at postoperative 60th min measurement in Group BF also.

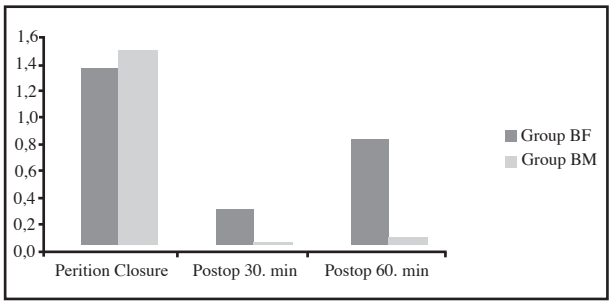


**Figure 2. Visual Analogue Scale scores of the groups.**

**Anesthesia determination parameters**

There was no statistically significant difference between groups at 1st min motor block level ($p>0.05$), however 3rd and 5th min motor block levels were significantly different between groups ($p<0.05$; Table 2). The Bromage score at 3rd min in Group LF was predominantly "1" and it was "2" in Group BF. The Bromage score at 5th min was predominantly "2" in Group LF and "3" in Group BF.

**Table 2. Motor block level of groups.**

| Time | Bromage score | Group LF n (%) | Group BF n (%) | P value |
|---|---|---|---|---|
| | 0 | 22 (55 %) | 12 (32 %) | |
| 1st min | 1 | 14 (35 %) | 14 (36 %) | 0.178 |
| | 2 | 4 (10 %) | 12 (32 %) | |
| | 0 | 6 (15 %) | 0 (0 %) | |
| 3th min | 1 | 20 (50 %) | 6 (15 %) | 0.015 |
| | 2 | 10 (25 %) | 20 (53 %) | |
| | 3 | 4 (10 %) | 12 (32 %) | |
| | 1 | 6 (15 %) | 0 (0 %) | |
| 5th min | 2 | 22 (55 %) | 10 (26 %) | 0.015 |
| | 3 | 12 (30 %) | 28 (74 %) | |

*Group LF: 7.5 mg (1.5 ml) hyperbaric levobupivacaine and 25 mcg (0.5 ml) fentanyl, Group BF: 7.5 mg (1.5 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl*

Max. motor block level and time to end of motor block were found to be higher in Bupivacaine (Group BF) group ($p<0.05$).

Onset of motor block time, time to max motor block, time to $T_4$ sensorial block, reversal of two dermatome, first analgesic need were similar in both groups (Table 3). Reversal of motor block was significantly different between groups, being mean value of Group BF was significantly higher than Group LF ($p<0.05$).

**Table 3. Anesthesia determination parameters of groups.**

| | Group LF mean±SD | Group BF mean±SD | P value |
|---|---|---|---|
| Onset of motor block (sec) | 135.00±75.70 | 97.89±42.82 | 0.069 |
| Onset of maximum motor block (sec) | 288.00±68.41 | 250.26±85.59 | 0.136 |
| Two dermatome regression (min) | 89.85±16.29 | 82.74±07.13 | 0.089 |
| First analgesic need (min) | 162.55±37.30 | 173.05±10.74 | 0.245 |
| Onset of T4 sensorial block (sec) | 345.00±134.69 | 304.26±110.99 | 0.279 |
| Intrathecal injection birth (min) | 22.00±3.76 | 19.11±06.02 | 0.079 |
| Operation (min) | 67.20±12.87 | 67.74±13.39 | 0.899 |

*Group LF: 7.5 mg (1.5 ml) hyperbaric levobupivacaine and 25 mcg (0.5 ml) fentanyl, Group BF: 7.5 mg (1.5 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl*

There was significant difference between "maximum sensorial block" levels between groups ($p<0.05$). In Group LF, sensorial block level was $T_2$ and $T_4$, in Group BF, it was $T_3$ and $T_4$ (Table 4). Sensorial block level distribution of groups at 1st, 3rd and 5th min were not different between group ($p>0.05$).

**Table 4. Comparison of maximum block level of groups.**

| | | Group LF n (%) | Group BF n (%) | P value |
|---|---|---|---|---|
| Sensorial | $T_2$ | 20 (50 %) | 2 (6 %) | 0.001 |
| | $T_3$ | 0 (0 %) | 18 (47 %) | |
| | $T_4$ | 18 (45 %) | 18 (47 %) | |
| | $T_5$ | 2 (5 %) | 0 (0 %) | |
| Motor | 1 | 6 (15 %) | 0 (0 %) | 0.044 |
| | 2 | 12 (30 %) | 4 (11 %) | |
| | 3 | 22 (55 %) | 34 (89 %) | |

*Group LF: 7.5 mg (1.5 ml) hyperbaric levobupivacaine and 25 mcg (0.5 ml) fentanyl, Group BF: 7.5 mg (1.5 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl*

There was significant difference between "maximum motor block" levels between groups ($p<0.05$). Besides, in group BF, max motor block level was predominantly "3" by Bromage score (Table 4).

Side effect distribution of groups are presented in Table 5 ($p<0.05$). Newborn apgar scores were similar in each group. The umbilical vein blood gas $PCO_2$ was higher and $PO_2$ was lower in bupivacaine group ($p<0.05$).

**Table 5. Side effect distribution of groups.**

| | Group LF n (%) | Group BF n (%) |
|---|---|---|
| Hypotension | 24 (60 %) | 20 (53 %) |
| Nausea | 22 (55 %) | 10 (26 %) |
| Vomiting | 14 (35 %) | 4 (11 %) |
| Ephedrine need | 14 (35 %) | 18 (47 %) |
| Bradycardia | 14 (35 %) | 6 (16 %) |
| Sedation | 14 (35 %) | 4 (11 %) |
| Pruritus | 26 (65 %) | 18 (47 %) |
| Headache | 4 (10 %) | 0 (0 %) |

*Group LF: 7.5 mg (1.5 ml) hyperbaric levobupivacaine and 25 mcg (0.5 ml) fentanyl, Group BF: 7.5 mg (1.5 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl*

## DISCUSSION

Recent trends of obstetric anesthesia show increased popularity of regional anesthesia among obstetric anesthetists. General anesthesia is associated with higher mortality rate in comparison to regional anesthesia [11]. Regional anesthesia has some risks; deaths are primarily related to excessive high regional blocks and toxicity of local anesthetics. Reduction in doses and improvement in technique to avoid higher block levels and heightened awareness to the toxicity of local anesthetics have contributed to the reduction of complications related with regional anesthesia [12].

Over the last decade, spinal anesthesia has been refined with the addition of opioids to local anesthetic solutions. It was reported that use of only local anesthetics in cesarean operation under spinal anesthesia, is not sufficient in prevention of nausea and visceral pain during uterus manipulation and periton closure, short duration of action and has disadvantages such as early need for analgesia [11-13]. The addition of morphine significantly prolongs post operative analgesia to 18-24 h, whereas the more lipophilic opioid such as sufentanil and fentanyl improve and prolong intraoperative anal-

gesia and reduce the amount of local anesthetics required to perform a sufficient dermatome spread and block intensity necessary for Caesarean section. By adding opioids to spinal anesthesia, a reduction in local anesthetic dose is possible. This reduction in local anesthetic requirements reduces the intensity and duration of motor blockade and allows patients to ambulate faster. Initial reports on low-dose spinal anesthesia suggest that this may also reduce maternal hypotension [14].

Today, 0.5% heavy bupivacaine is most commonly used for spinal anesthesia for caesarean section [3]. Recent studies have claimed successful anesthesia with very low doses of intrathecal bupivacaine (5-9 mg) when co administered with opiods [7,15,16]. Kiran and Singal advocated the use of 7.5 mg bupivacaine for Caesarean section as this dose was associated with a decreased incidence of hypotension ,but again, a large number of patients rated the analgesic quality as poor [17]. Ginosar et al. reported $ED_{50}$ and $ED_{95}$ of hyperbaric bupivacaine in cesarean section with combined spinal epidural technique is 7.6 mg and 11.2 mg, respectively [18]. In our study, anesthesia was 95 % successful with 25 mcg fentanyl added to 7.5 mg hyperbaric bupivacaine. Only in two patients, it was not sufficient and local anesthetics were administered.

Due to lower cardiovascular side effect and central nervous system toxicity, use of levobupivacaine as pure S(-) enantiomer of bupivacaine is progressively increased [5,19]. Epidural levobupivacaine has the advantage of decreased cardio toxicity in cases of accidental intravascular injection [20]. Parpaglioni et al reported minimum intrathecal levobupivacaine dose to be 10.58 mg in cesarean section [21]. Alley et al evaluated three intrathecal doses of levobupivacaine and bupivacaine (4, 6 and 8 mg) in healthy volunteers and found no differences in clinical profile of sensory and motor blocks and recovery from spinal anesthesia [22]. In some studies, levobupivacaine and racemic bupivacaine showed undistinguishable clinical profile in spinal anesthesia [23,24].

In selection of local anesthetics, it is desired that the agent's onset of action is short, duration of action is longer and sensorial block level to motor block level is higher. Camorcia et al. reported that intrathecal 0.5 % levobupivacaine had weaker motor block potency than 0.5 % bupivacaine in elective cesarean cases with CSE anesthesia technique [6]. Similarly Vercauterenet et al. performed a study on patients who received either 0.125 % levobupivacaine or 0.125 % racemic bupivacaine and found that levobupivacaine led to less motor impairment compared to racemic bupivacaine in intrathecal labor analgesia [25]. In our study, levobupivacaine had lesser motor potency. Bromage score at 3rd and 5th min were 1-2 in levobupivacaine and 2-3 in bupivacaine. On the other hand, max sensorial block level was found to be higher in levobupivacaine group. In levobupivacaine group, $T_2$ was predominant at sensorial block, and in bupivacaine group, $T_3$ was more. Preoperative VAS scores were similar in both groups, whereas postoperative 30th and 60th min VAS scores were lower in bupivacaine group.

Hypotension incidence in cesarean cases were reported to be 45 % and in its prevention, fluid replacement, left lateral decubitus position and use of vasoconstrictors were recommended [26,27]. In our study, it was 60 % in levobupivacaine and 53 % in bupivacaine group. Sympathetic block due to supine position and patient's head down position were probably affected in our study.

Intrathecal opioids administration has side effects such as nausea, vomiting, pruritus, sedation, respiratory depression and urinary retention [28]. Highly lipid soluble opioids cause temporary pruritus whereas intrathecal morphine causes long acting and intensive pruritus [28]. In our study, pruritus incidence was higher in LF group, however it was not intense to be treated.

There was significantly higher number of ASA II cases in group BF. This difference is due to inclusion of ASA II cases with respiratory system disor-

ders without requirement for any treatment which is a factor for regional anesthesia preference.

It was reported that fentanyl or morphine added to intrathecal bupivacaine did not affect apgar score and newborn blood gas values in cesarean cases. Umbilical cord blood pH and acid-base balance is objective predictor of neonatal well-being [29]. In our study, apgar score analysis was not significantly different between groups, umbilical vein $pCO_2$ was higher in bupivacaine group and $pO_2$ was lower. However these values were within normal ranges. Thus, we concluded that administration of green mask $O_2$ support to all cases in cesarean cases with regional anesthesia will be better for newborns even though $SpO_2$ values are within normal ranges.

In the study of Bremerich et al. fixed doses of intrathecal hypertonic levobupivacaine 0.5 % (10 mg) and bupivacaine 0.5 % (10 mg) combined with either intrathecal fentanyl (10 and 20 microg), or sufentanil (5 microg) were compared in terms of sensory and motor block characteristics. However we compared lesser 7.5 mg hyperbaric levobupivacaine and 7.5 mg bupivacaine combined with higher fentanyl dose (25 mcg) than that was used in study of Bremerich et. al. [30]. Also in the study of Gautier P et al, different doses than that of our study were used [24].

Intrathecal 7.5 mg hyperbaric levobupivacaine and 25 mcg fentanyl combination is good alternative to 7.5 mg bupivacaine - 25 mcg fentanyl combination in cesarean surgery as it is less effective in motor block, but it maintains hemodynamic stability at higher sensorial block levels.

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