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Original Article

# Baricity of Bupivacaine on Maternal Hemodynamics after Spinal Anesthesia for Cesarean Section: A Randomized Controlled Trial

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## Abstract

**Background:** After spinal anesthesia, patients undergoing cesarean section are more likely to develop hemodynamic changes. The baricity of local anesthetic has an important role on spinal blockade effects. The aim of this study was to compare the isobar and hyperbaric bupivacaine 0.5% plus fentanyl on maternal hemodynamics after spinal anesthesia for C/S.

**Methods:** In this double-blind study, 84 healthy pregnant women undergoing C/S using bupivacaine 0.5% isobar (study group, n=42) or hyperbaric (control group, n=42) for spinal anesthesia were scheduled. The study was conducted from 21 April 2014 to 21 November 2014 at Al-Zahra Hospital, Tabriz, Iran. Parameters such as maternal hemodynamics, block characteristics, side effects, and neonatal Apgar scores were recorded. Data were analyzed using the SPSS software by performing chi-square test, Fisher's exact test, one-way ANOVA, Mann-Whitney U-test, and student's *t* test.

**Results:** The incidence of hypotension in the isobar group was lower than the hyperbaric group, although it was not statistically significant (40.47% vs. 61.9%, P=0.08). The duration of hypotension was shorter in the study group (1.6±7.8 min vs. 7.4±12.5 min, P=0.004). The dose of ephedrine was lower in the study group (2.4±6.6 mg vs. 5.3±10.7 mg, P=0.006). The main maternal side effect is sustained hypotension that was seen in 0 patients of the isobar and 7 (16.66%) of hyperbaric groups (P=0.006). None of the neonates had Apgar score≤7 at 5 min of delivery (P=1.0). Sensory and motor block duration was shorter in the study group (P=0.01).

**Conclusion:** Isobaric bupivacaine is associated with more hemodynamic stability and shorter sensory and motor blockade in mothers under spinal anesthesia for C/S.

**Trial Registration Number:** IRCT201401287013N7

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**Keywords** ● Cesarean section ● Anesthesia ● Spinal ● Bupivacaine ● Hypotension

## What's Known

- The most common local anesthetic for spinal anesthesia is hyperbaric bupivacaine. However, hypotension, particularly during cesarean section, is common.
- Adding dextrose to the solution of bupivacaine (hyperbaric form) may be associated with a higher incidence of hypotension after spinal anesthesia.
- The specific influence of the baricity of the local anesthetic on the efficacy of the block is controversial.

## What's New

- We found that the use of plain bupivacaine (without adding dextrose) was associated with maternal hemodynamic stability after spinal anesthesia for cesarean section.

## Introduction

Hypotension is the most common effect of neuraxial anesthesia, particularly in obstetric patients. The prevalence in patients under cesarean section (C/S) is 80-90%. Hypotension causes unpleasant symptoms such as nausea, vomiting, unconsciousness, respiratory depression, and cardiac arrest in mothers. In severe and prolonged conditions, it leads to the impairment of uterine perfusion and ultimately fetal acidosis and neonatal depression.[1-4]

The required spinal block height for C/S is at $T_{4-6}$ dermatome level. In order to avoid expanded sympathetic block and hypotension, the spread of local anesthetic in subarachnoid space should not be higher than the $T_4$ dermatome level.[5]

The most common local anesthetic for spinal anesthesia in patients under obstetric and non-obstetric surgery is bupivacaine that can be used as isobaric or hyperbaric solution.[1,4,6] Cesarean section is usually performed by the spinal anesthesia of hyperbaric bupivacaine. This has been reported to be associated with an increased incidence of severe hypotension.[7] Isobar bupivacaine is not commonly used for spinal anesthesia, but could be a good alternative for obstetric patients due to lower complications than the hyperbaric solution.[8] Besides to volume, the concentration and dose of local anesthetic, as well as the baricity of solution might affect spinal block profile.[1,9-12]

A study by Rofaeel et al.[13] showed an earlier onset of analgesia and higher sensory block level with isobar compared to hyperbaric bupivacaine during combined spinal-epidural analgesia for vaginal delivery; without statistically significant differences in the incidence of hypotension. Solakovic[14] reported that the baricity of local anesthetic was effective on the height of spinal block for C/S and hyperbaric bupivacaine was associated with higher incidence of hypotension than the isobar solution. In contrast, in a randomized study, Hallworth et al.[15] observed that the incidence of hypotension and ephedrine use were greater in the isobaric bupivacaine than the hyperbaric bupivacaine.

The specific influence of the baricity of local anesthetics on the efficacy of the spinal block is controversial. In the literature,[1] additional studies are recommended to determine the effect of baricity of spinal local anesthetic on the spinal block characteristics, especially in obstetric patients. Considering the scarcity of publications and conflicting results on this topic, this study was instigated to compare isobaric and hyperbaric bupivacaine 0.5% plus fentanyl on maternal hemodynamics after spinal anesthesia for C/S.

## Patients and Methods

In this double-blind randomized clinical trial, 84 eligible parturients for elective cesarean section under spinal anesthesia were enrolled. The study was conducted at Al-Zahra Hospital (Tabriz, Iran) during April 2014 to November 2014. The inclusion criteria were healthy pregnant women with term singleton pregnancy, age range18-40 years, and non-emergency cesarean section. The exclusion criteria were patients with systemic and psychological disorders, pre-eclampsia, placental disorders, emergency C/S, weight>85 kg, height<150 cm, any contraindications for spinal anesthesia, and allergy to local anesthetic. The patients did not receive premedication. Ethical approval was obtained from the Research Vice Chancellor of Tabriz University of Medical Sciences and all participants gave their written informed consent.

The sample size was determined based on the preliminary data from an earlier study.[15] The primary outcome of this study was a reduction in the incidence of hypotension. We determined that an effective sample size of 84 (42 per group) would be required to provide the statistical power of 80% (two-tailed test, $\alpha$=0.05), in order to detect a 15% difference in the incidence of hypotension between the two groups.

The patients fasted for 6 hours. In the operating theatre, routine standard monitoring with non-invasive blood pressure (NIBP), electrocardiogram (ECG), and pulse oximeter was established. Baseline measurements were performed 5 minutes before spinal anesthesia. Ringer solution at a rate of 10-20 ml/kg was administered to all patients before the induction of spinal anesthesia. Under aseptic conditions, with the patient in sitting position, lumber puncture was performed at the $L_{2-3}$ or $L_{3-4}$ interspaces.

In terms of the baricity of local anesthetics, the patients were randomly categorized into two groups using a coded and sealed envelope technique (figure 1). The study group (n=42) was given isobar (Bupivacaine MYLAN S.A.S,100 mg/20ml, CEDEX, France) and the control group (n=42) received hyperbaric (Marcaine 0.5% Spinal Heavy, Astra Zeneca, CENEXI, France). Using a 25G Quincke spinal needle, 10 mg bupivacaine 0.5% plus 15 µg fentanyl was injected within 5-10 seconds. The total volume of the solution was 2.5 ml. Hyperbaric bupivacaine was available in 4 ml ampoules. Each ampoule contained 5 mg/ml solution (0.5%) and 80 mg dextrose (8%). Isobar agent was supplied in 20 ml vials. Each milliliter of the solution contained 5 mg bupivacaine HCL. The solutions were freshly prepared in numerically labeled syringes at the beginning of each spinal anesthesia by an anesthesiologist who was not involved in the study variables record. A nurse anesthetist, who was also blind to the medication, administered the solution. Patients were immediately positioned in supine, kept at 15 degrees left lateral tilt, and slight (10 degrees) leg-up position until the delivery of neonate. Patients were given oxygen

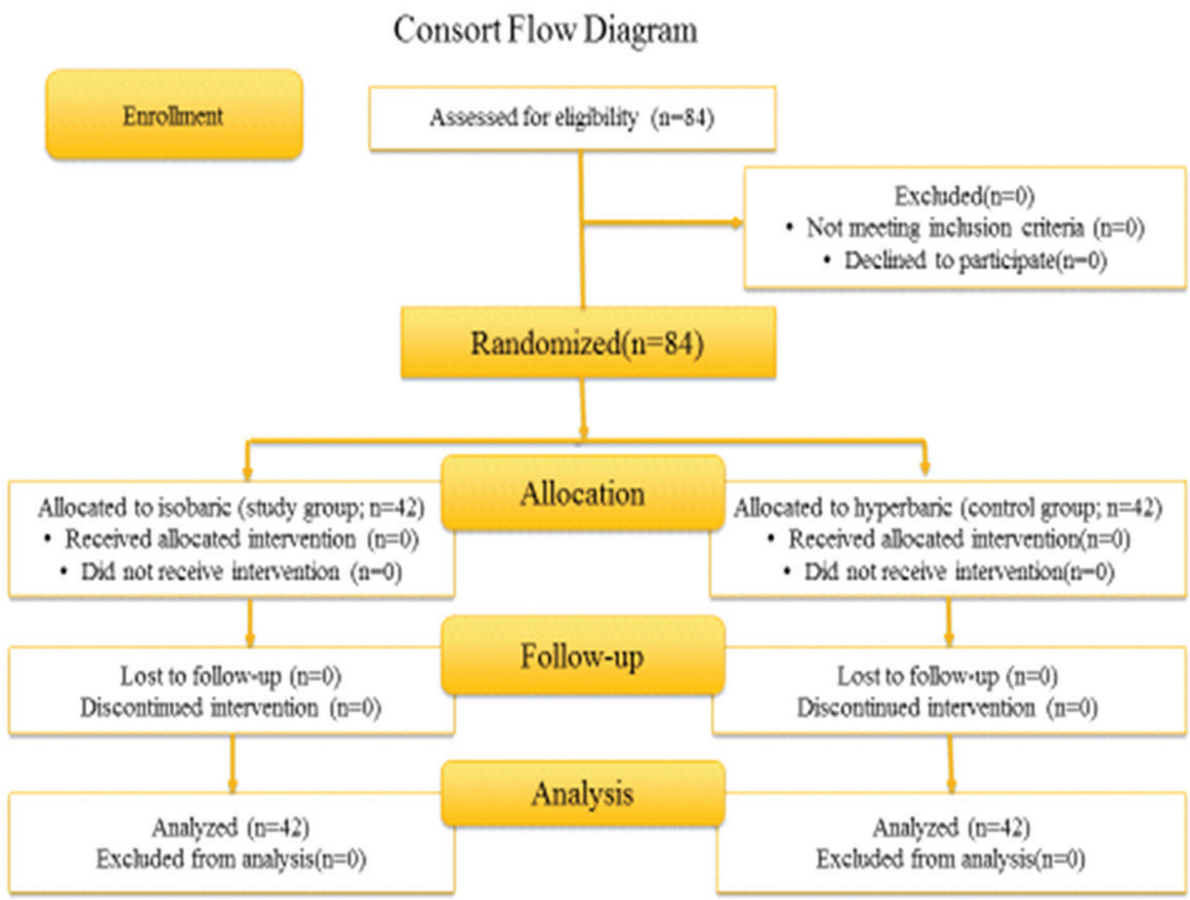


**Figure 1:** Shows the flowchart of patients enrolled in the study.

at the flow rate of 4-6 L/min by face mask. The level of sensory block was assessed using the pinprick sensation method. The level of $T_{5-6}$ was considered adequate for surgery.

Maternal hemodynamic parameters (systolic blood pressure(SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR)) were recorded every 2 minutes up to the delivery of the neonate and then every 5 minutes until the end of surgery. SBP<100 mmHg or a decrease beyond 25% from the baseline levels was treated by incremental i.v. doses of ephedrine 5 mg or phenylephrine 50 µg. If bradycardia (HR<60/min) occurred, atropine 0.5 mg was injected. The patients who had severe bleeding were excluded from the study. The highest level of sensory block, motor block scale (by Bromage et al.[9] scoring), vasopressor requirements, total amount of fluid administered, incidence of side effects (nausea, vomiting, agitation, respiratory depression, and loss of consciousness), neonatal Apgar scores at 1 and 5 minutes, and duration of sensory and motor block were recorded. Intravenous metoclopramide 5mg and midazolam 1mg were administered to treat vomiting and agitation, respectively. Patients were treated with assisted ventilation if they had respiratory depression or loss of consciousness. Two anesthesiologists; one for preparing the study solutions and management of anesthesia, and the other with a medical student (unaware of the study group) were in charge of recording patients' data.

Data are presented as mean±SD, median (range), and counts (number). The mean was analyzed using the student's *t*-test and median by the Mann-Whitney U-test, Fisher's exact test, and chi-square test. One-way ANOVA test was used for quantitative variables. All analyses were performed using the SPSS statistical software, version 15 (SPSS Inc., Chicago, IL, USA). The level of statistical significance for all tests was P≤0.05.

## Results

As shown in table 1, the groups were comparable in terms of age, weight, height, C/S causes, parity, and duration of operation. The highest level of sensory block in both groups was $T_{3-6}$ dermatome. The majority of patients (95.2% in the isobaric and 85.7% in the hyperbaric groups) had level $T_5$ sensory block (P=0.26). Sensory block of $T_3$ level was seen in 2 (4.8%)

and 7 (16.16 %) patients of the study and control groups, respectively (P=0.03). All patients had complete motor block at the beginning of the surgery.

Hemodynamic variables are shown in table 2. There were no significant differences in terms of baseline HR, SBP, DBP, MAP and $SpO_2$ between the two groups. The incidence of hypotension in the hyperbaric group was higher than the isobar group, although not statistically significant. The time to first hypotensive episode and the lowest SBP were not significantly different between the two groups. The duration of hypotension in the hyperbaric group was significantly greater than the isobar group. Similarly, the need for vasopressor was significantly more common following hyperbaric bupivacaine. The groups did not differ with regard to the amount of total i.v. fluid.

The incidence of spinal anesthesia side effects is presented in table 3. The most common complication was sustained hypotension that occurred in 16.6% of patients in the hyperbaric group. The prevalence of bradycardia, nausea, vomiting, and agitation was equal in both groups. Neonatal Apgar score was comparable between the groups. None of the neonates had Apgar score≤7 at 5 minutes of delivery (table 3). The duration of sensory (63.48±7.31 min vs. 67.12±5.7 min, P=0.01) and motor block (69.02±7.1 min vs. 77.0±5.3 min, P=0.01) were shorter in the study group.

## Discussion

The results of this study showed that when spinal anesthesia was performed with 10 mg isobaric bupivacaine plus fentanyl, it produced greater hemodynamic stability than the same dose of hyperbaric solution in patients undergoing C/S.

Previous studies have shown that the incidence of hypotension after spinal anesthesia was 40-100%. The incidence of hypotension in

**Table 1:** Demographic data between the groups

| | Isobaric group (n=42) | Hyperbaric group (n=42) | P |
|---|---|---|---|
| Age (yr) | 28.26±5.65 | 30.05±5.72 | 0.57 |
| Weight (kg) | 78.63±10.20 | 78.86±10.16 | 0.93 |
| Height (cm) | 159.60±4.01 | 159.80±3.48 | 0.79 |
| Parity | 1.95 (1-4) | 2.05 (1-5) | 0.14 |
| Cause of C/S (%) | | | |
| CPD | 6 (14.3) | 10 (23.8) | 0.62 |
| Repeat | 25 (59.5) | 26 (62.0) | 0.74 |
| Others | 15 (35.7) | 6 (14.20) | 0.35 |
| Duration of surgery (min) | 50.86±12.70 | 56.24±12.40 | 0.51 |

Data are presented as mean±SD, median (interquartile range), and number (%). CPD: Cephalopelvic disproportion

**Table 2:** Hemodynamic variables between the groups

| | Isobaric group (n=42) | Hyperbaric group (n=42) | P |
|---|---|---|---|
| Baseline hemodynamic data | | | |
| SBP (mmHg) | 128±11.30 | 124±10.30 | 0.16 |
| DBP (mmHg) | 80±9.80 | 77.6±11.5 | 0.21 |
| MAP (mmHg) | 94.9±9.7 | 92.4±10.2 | 0.34 |
| HR (bmp/min) | 99±17 | 101±16 | 0.75 |
| SpO2 (%) | 97.16±0.89 | 97.13±0.93 | 0.96 |
| Hypotension (%) | 17 (40.47) | 26 (61.90) | 0.08 |
| First hypotension episode (mmHg) | 79.8±10.8 | 79.6±9.5 | 0.88 |
| Time of first hypotension (min) | 4.0±1.7 | 3.89±1.40 | 0.82 |
| Lowest hypotension value (mmHg) | 76.3±9.6 | 72.0±9.3 | 0.14 |
| Duration of hypotension (min)* | 7.8±1.6 | 12.5±7.4 | 0.004 |
| Vasopressor use (%)* | 17 (40.5) | 33 (78.57) | 0.02 |
| Ephedrine (%) | 15 (35.71) | 19 (45.2) | 0.78 |
| Phenylephrine (%)* | 2 (4.76) | 14 (33.34) | 0.001 |
| Ephedrine dose (mg)* | 6.6±2.4 | 10.7±5.3 | 0.006 |
| Phenylephrine dose (mg) | 110±22.3 | 121±42.5 | 0.46 |

Data are presented as mean±SD and number (%). SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, SpO2: Peripheral capillary oxygen saturation. *P<0.05

| **Table 3:** Maternal complications and neonatal variables between the groups | | | |
|---|---|---|---|
| | **Isobaric group (n=42)** | **Hyperbaric group (n=42)** | **P** |
| Maternal complications | | | |
| Sustained hypotension (%)* | 0 (0) | 7 (16.66) | 0.006 |
| Bradycardia (%) | 3 (7.14) | 3 (7.14) | 1.00 |
| Nausea-Vomiting (%) | 4 (9.50) | 5 (11.90) | 0.72 |
| Loss of consciousness (%) | 0 (0) | 1 (2.38) | 0.32 |
| Respiratory depression (%) | 0 (0) | 1 (2.38) | 0.32 |
| Agitation (%) | 3 (7.14) | 4 (9.50) | 0.75 |
| Neonatal variables | | | |
| Apgar score 1 min | 9.12±0.55 | 8.94±0.78 | 0.33 |
| Apgar score 5 min | 9.90±6.5 | 80±0.48 | 0.36 |
| Apgar score≤7 at 1 min | 0 | 2 (4.76) | 0.49 |
| Apgar score≤7 at 5 min | 0 | 0 | 1.00 |

Data are presented as mean±SD and number (%). *P<0.05

cesarean section is higher.[1-5] In this study, the overall incidence of hypotension was 51.1%, meaning that the prevalence of hypotension is still high. In our study, hypotension was developed in 40.47% and 61.90% of patients in isobaric or hyperbaric bupivacaine group, respectively. We could not prevent hypotension completely; however, we were able to reduce its incidence by about 20% in the isobaric group compared with the hyperbaric group. The ephedrine requirement was reduced in patients given isobaric bupivacaine, and their systolic and diastolic blood pressures remained more stable with respect to baseline blood pressures compared with patients in the other group. The main reasons for hypotension after spinal anesthesia are rapid blockage of sympathetic nerves and aortocaval compression leading to decreased systemic vascular resistance (SVR), decreased venous return because of blood pooling in the peripheral veins, and reduced cardiac output.[16] The decrease in sympathetic efferent activity after spinal anesthesia is related to the dose of bupivacaine, and intrathecal fentanyl does not lead to further depression in the sympathetic efferent activity.

Studies have indicated that when the intrathecaly given dose of local anesthetic is reduced by adding the opioids, it reduces the incidence of hypotension after spinal anesthesia.[17] The reason for the lower incidence of hypotension in our study could be related to adequate preloading of patients and particularly the use of low-dose and low-volume intrathecal solution. Low doses of the isobar or hyperbaric local anesthetic block fewer segments and likely limit the spread of sympathetic blockade.[12,18]

In the present study, the incidence and duration of hypotension were high in the hyperbaric group. Additionally, the onset of hypotension in the control group was more rapid compared with the study group, although not statistically significant. In a randomized clinical trial, Rofaeel et al.[13] observed that the incidence of hypotension was greater in women undergoing labor analgesia, who were randomly assigned to receive isobaric bupivacaine combined with fentanyl as the spinal component of a combined spinal-epidural analgesia in the sitting position, compared with that of the hyperbaric bupivacaine. Critchly et al.[7] observed that the use of heavy solutions of bupivacaine (hyperbaric solution) for subarachnoid block was associated with an increased incidence and more rapid onset of hypotension and heart rate changes, a decrease in central venous pressure (CVP), and a greater need for early corrective treatment of hypotension by vasopressor agents during the initial phase of subarachnoid block. Their findings were very similar to the results of the present study. They also found that the cardiovascular effects of spinal block seemed to be related to more rapid sensory blockade; a parameter that we did not evaluate.

Other studies have shown that hypotension after spinal anesthesia is due to higher level block and assigned sympathetic denervation path.[6,8,10,11] Hussain et al.,[8] in a randomized clinical trial in patients undergoing endoscopic urologic surgery under spinal anesthesia with hyperbaric or isobaric bupivacaine and low dose fentanyl, reported that isobaric bupivacaine can provide a dense block for surgery with minimum hemodynamic effects. In the present study, hemodynamic changes were higher in the hyperbaric group such that the number with arterial hypotension and requiring vasopressors intraoperatively was higher; a fact attributed to the higher density of bupivacaine. Since the doses of bupivacaine were the same in both groups, other confounding factors in the occurrence of hypotension (e.g. oxytocin infusion) were similar.[18]

Research studies have reported that the baricity of local anesthetic solution affects the level of spinal block. Anesthesia for caesarean section should be $T_{4-6}$ dermatome. The majority of patients in both groups had level $T_{4-6}$ sensory block. The sensory block of $T_3$ level was seen to be higher in patients of the control than the study groups. These findings indicate that sensory block in the isobaric group was in the healthy range and suitable for caesarean section. When spinal anesthesia is performed in sitting position and then the patient is immediately positioned in supine state, hyperbaric solution moves to cephalad. The isobaric solution is intended to remain at injection level, but hyperbaric solution is intended to move the dependent site of supine with normal spinal anatomy. The highest apex of thoraco-lumber curve is at $T_4$ level. Therefore, hyperbaric solution causes anesthesia upon higher than $T_4$ level.[8,13,15,19] In the present study, more patients of the hyperbaric group had sensory block level at $T_3$ than the study group. Therefore, the hyperbaric solution was more associated with hypotension. Because the block does not extend into the upper thoracic level, it leads to little sympathetic block. These findings also correspond with the studies by Solakovic.[6,14] However, a study by Rofaeel et al.[13] showed that when intrathecal isobaric bupivacaine is used for delivery analgesia, it induces sensory block higher than the hyperbaric solution. A study by Halworth et al.[15] showed that baricity had no effect on the spread of sensory levels for bupivacaine.

Bradycardia occurred in 3 (7.14%) patients of each group. Atropine was used in all patients with bradycardia. Toptas et al.[20] compared the effects of hyperbaric and isobaric bupivacaine spinal anesthesia on hemodynamics and heart rate variability in non-obstetric surgery. They concluded that the incidence of hypotension was not different between the two groups, but hyperbaric bupivacaine caused significantly greater heart rate variability.

Vasopressors have been effectively used for the treatment of hypotension after spinal anesthesia. Ephedrine is the most common agent.[1-3,7] In this study, greater doses of ephedrine were used in the control group due to a higher incidence of hypotension.

The duration of sensory and motor block was prolonged in the hyperbaric group, indicating that the duration of block is related to baricity of spinal anesthesia.[15] However, Punshi et al.[19] found that sensory block level regression was delayed in the isobaric group and prolonged the duration of block. Srivastava et al.[21] did not find any difference between the two groups with respect to duration of the block despite a difference in the baricity of local anesthetic solution. They suggested that the spread of spinal solution is not dependent on the density of bupivacaine. Therefore, there was no difference in the onset time, highest level, and recovery of sensory block between the two groups of patients undergoing cesarean section under spinal anesthesia with hyperbaric or isobaric bupivacaine.

Although the incidence of hypotension was significantly different between the two groups, it could easily be treated with vasopressors and did not cause adverse effects on the mother and fetus/neonate. In this study, the conditions of the neonates were good and similar in both groups. None of the two groups of neonates had an Apgar score≤7.

Our study has a few limitations. Firstly, the onset of sensory block was not evaluated. Martin et al.[22] observed that sensory and motor block developed more rapidly with the isobaric bupivacaine. However, the duration of sensory block with either form of bupivacaine was similar. In addition, Helmi et al.[23] showed that isobaric bupivacaine produced more rapid onset and longer duration when compared to hyperbaric bupivacaine. They did not show significant differences in the incidence of hypotension between the two groups. Secondly, the temperature of local anesthetic has an important role in the spread of agents within the cerebrospinal fluid (CSF) and thus influences the extent of spinal block. The temperature of the solution should equilibrate to the temperature of CSF.[21] However, a bupivacaine that could be stored at room temperature was used in this study.

## Conclusion

Isobaric bupivacaine produces less incidence and duration of hypotension, lower use of vasopressors, and shorter sensory and motor block than the hyperbaric bupivacaine after spinal anesthesia for C/S.

**Conflict of Interest:** None declared.

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