

# The effects of hyperbaric or isobaric bupivacaine on bispectral index in spinal anesthesia for cesarean section

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**Background:** Hyperbaric and isobaric bupivacaine has been shown to reduce bispectral index (BIS) during spinal anesthesia. The aim of this study was to compare the effect of isobaric bupivacaine and hyperbaric bupivacaine on the BIS during cesarean section with spinal anesthesia. **Materials and Methods:** In this double-blind randomized controlled clinical trial, 84 pregnant women with ASA (American Society of Anesthesiologists) class I or II were randomly assigned to receive isobaric or hyperbaric bupivacaine. BIS was measured using electroencephalography (EEG) and recorded at the baseline and 5th, 10th, 15th, 30th, 45th, 60th, 90th and 120th minutes after spinal injection. The heart rate (HR), mean arterial pressure (MAP), signal quality index (SQI), electromyography (EMG) and the temperature were also recorded during surgery. **Results:** From recruited subjects, 41 completed the study in each group and their data were analyzed. The BIS score began to reduce until 30<sup>th</sup> minute for isobaric bupivacaine and 45<sup>th</sup> minute for hyperbaric bupivacaine after spinal injection. The recorded BIS was not significantly different between two groups at all the time points. Difference of BIS from baseline was not significant between two groups at most time points except for the 45<sup>th</sup> minute after injection that it was  $5.9 \pm 9$  vs.  $2.7 \pm 4.6$  for hyperbaric and isobaric bupivacaine, respectively ( $p = 0.047$ ). The changing trend was not significantly different between groups with hyperbaric and isobaric bupivacaine. **Conclusion:** According to the present study, the BIS score during surgery began to decrease when the patients were injected spinally by both of these drugs. The greatest decrease from baseline BIS values occurred at 30 and 45 minutes after induction of spinal anesthesia. However, hyperbaric or isobaric bupivacaine did not have different effects on the BIS during spinal anesthesia.

**Key words:** Anesthesia, Hyperbaric, Isobaric, Bupivacaine, Bispectral Index, Depth, Spinal.

## INTRODUCTION

Spinal anesthesia with a sedative drug may affect patient's consciousness, but one study has shown that patients undergoing spinal anesthesia without the sedatives may suffer from decreased level of consciousness.<sup>1</sup> Spinal anesthesia is widely used for cesarean section. Regional anesthesia techniques have several advantages, including a decreased risk of failed intubation and aspiration of gastric contents, avoidance of depressant agents, and the ability of the mother to remain awake and enjoy the birthing experience. In addition, it has been suggested that blood loss is reduced under regional anesthesia for cesarean delivery. Spinal anesthesia has been found to be faster, more cost-effective and provide a superior block.<sup>2</sup> Patients undergoing cesarean section showed decreased level of consciousness with spinal anesthesia.<sup>3</sup>

Bispectral score (BIS) is EEG derived parameters related to the level of sedation and loss of consciousness.<sup>3-6</sup> BIS was recognized as a method by

which the anesthesiologists were able to determine the depth of anesthesia in high-risk surgeries for the first time.<sup>5-9</sup> Some factors affect the depth of spinal anesthesia including pregnancy, additional drugs and baricity.<sup>4,6,8,10</sup> Pregnant women demonstrate increased sensitivity to regional anesthetics. From early pregnancy, when neuraxial anesthesia is administered, women require less local anesthetic than non pregnant women do reach a given dermatomal sensory level.<sup>2,11,12</sup>

It was previously reported that the BIS value during spinal anesthesia with isobaric bupivacaine is reduced with intrathecal fentanyl but not with intravenous or epidural fentanyl.<sup>6</sup> The BIS values in patients who received intrathecal isobaric bupivacaine with fentanyl were lower than those with intrathecal hyperbaric bupivacaine and fentanyl.<sup>10</sup> Intrathecal hyperbaric bupivacaine-fentanyl produces a longer alertness than single hyperbaric bupivacaine.<sup>3</sup> There are no studies evaluating intrathecal isobaric and hyperbaric bupivacaine alone and without fentanyl with respect

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to BIS values. The aim of this study was to compare the effect of isobaric bupivacaine and hyperbaric bupivacaine on the BIS during cesarean section with spinal anesthesia.

## MATERIALS AND METHODS

Following ethics committee approval and obtaining informed patient consent, 84 pregnant women undergoing elective cesarean section were recruited. This double-blind randomized controlled clinical trial was performed in Beheshti Medical Center, Isfahan, Iran, during the period from March 2008 to April 2011. Inclusion criteria were ASA I or II (American Society of Anesthesiologists), no cardiovascular disease, no history of diabetes, no previous pregnancy complications and no history of twin pregnancy. Exclusion criteria were any significant history of maternal medical or obstetric illnesses.

All patients were fasted for 8 hours preoperatively and infused intravenous preload of 10cc/kg Ringer's lactate solution before surgery. Intraoperative monitoring included pulse oximetry, automated blood pressure cuff, lead II electrocardiogram and capnograph.<sup>13-15</sup>

The operating theatre nurse assistant used randomization protocol to assign participants to their respective groups. Patients were randomly assigned to receive isobaric or hyperbaric bupivacaine. Randomization was done by a table of random numbers with minimization for age, medical and psychiatric status. Both patient and anesthetist were blind to treatment.

Before spinal anesthesia, the cerebral state monitoring (CSM) electrodes were placed in the fronto-temporal regions as recommended by the manufacturer (CSM, New version, Danmeter Co, Denmark) which used for measurement of BIS values, signal quality index (SQI) and electromyography (EMG). To reduce skin/electrode impedance, the skin over the forehead was cleaned with an alcohol-impregnated skin wipe. The BIS values were only considered valid when SQI was above 50%. If SQI was < 50% for longer than 20% of the total study period, all data for the patient were excluded from analysis.

Lumbar puncture was performed in the sitting position. A 25 gauge spinal needle (pencil point, Pajunk, Germany) was introduced into the subarachnoid space at the L3-L4 lumbar level midline approach with the needle orifice cephalad. Cerebrospinal fluid was aspirated and the ready fluid 2.5 mL hyperbaric 0.5% dissolved in 8.25% glucose solution<sup>13</sup> (Marcaine 5%, Mylan Co, France) or 2.5 mL isobaric bupivacaine 0.5%<sup>6</sup> (Mylan co, France) was injected to subarachnoid space over the period of 15 seconds, with no barbitate. Patient was set to the left lateral position.

The maximum level of sensory motor block assessed by pin prick test after spinal anesthesia. Motor block was assessed by modified bromage score (0: not motorless, 1: inability to flex the hip, 2: inability to flex the knee, 3: inability to flex ankle). After establishment of T4 block with pin prick test and confirmation of anesthesia, cesarean section was done. The study solutions were prepared by another researcher not involved in patient care, then injected immediately afterwards. The spinal needle was withdrawn and patient were repositioned supine with elevation of head (15-20°).

BIS, SQI, EMG, heart rate (HR), mean arterial pressure (MAP) and the core temperature (evaluated by tympanic thermometer, braun, IRT 3020, Type = 6012, Thermoscan, Kronberg, Germany) was recorded at the baseline and 5<sup>th</sup>, 10<sup>th</sup>, 15<sup>th</sup>, 30<sup>th</sup>, 45<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> minutes after spinal injection. If SBP was < 20% below baseline or < 100 mmHg, intravenous (IV) ephedrine 5mg was given incrementally. If heart rate was less than 50 beats/min, 0.5mg atropine sulfate was administered IV.<sup>3,13,14</sup>

The sample size was based on the previous studies, 0.90 powers and  $\alpha$  error of 0.05. It was calculated to be 84. The analyses were performed based on Mann-Whitney test and independent Student's t-test for quantitative variables. All analysis was done using SPSS software (version 18, SPSS Inc., Chicago, IL, USA).<sup>16</sup> A p value of < 0.05 was considered statistically significance for all analyses. The quantitative data are presented as mean  $\pm$  SD.

## RESULTS

The hyperbaric bupivacaine group included 42 subjects with mean age of  $28.6 \pm 5.7$  years and the isobaric bupivacaine group consisted of 42 patients with mean age of  $28.2 \pm 5.7$ . Two groups did not have significant difference at baseline characteristics and baseline conditions (Table 1). The heart rate, mean arterial pressure changes, temperature, EMG and SQI did not have significant differences at the baseline and 5<sup>th</sup>, 10<sup>th</sup>, 15<sup>th</sup>, 30<sup>th</sup>, 45<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup> and 120<sup>th</sup> minutes after spinal injection between two groups. From recruited subjects, 41 completed the study in each group and underwent analysis. One subject was excluded due to SQI < 50% (Figure 1).

The recorded BIS was not significantly different between two groups at all the time points (Table 2). Difference of BIS from baseline was not significant between two groups at most time points but this difference was statistically significant at the 45<sup>th</sup> minute after injection ( $p = 0.047$ , Table 3). The changing trend was not significantly different between groups with hyperbaric and isobaric bupivacaine (Figure 2).

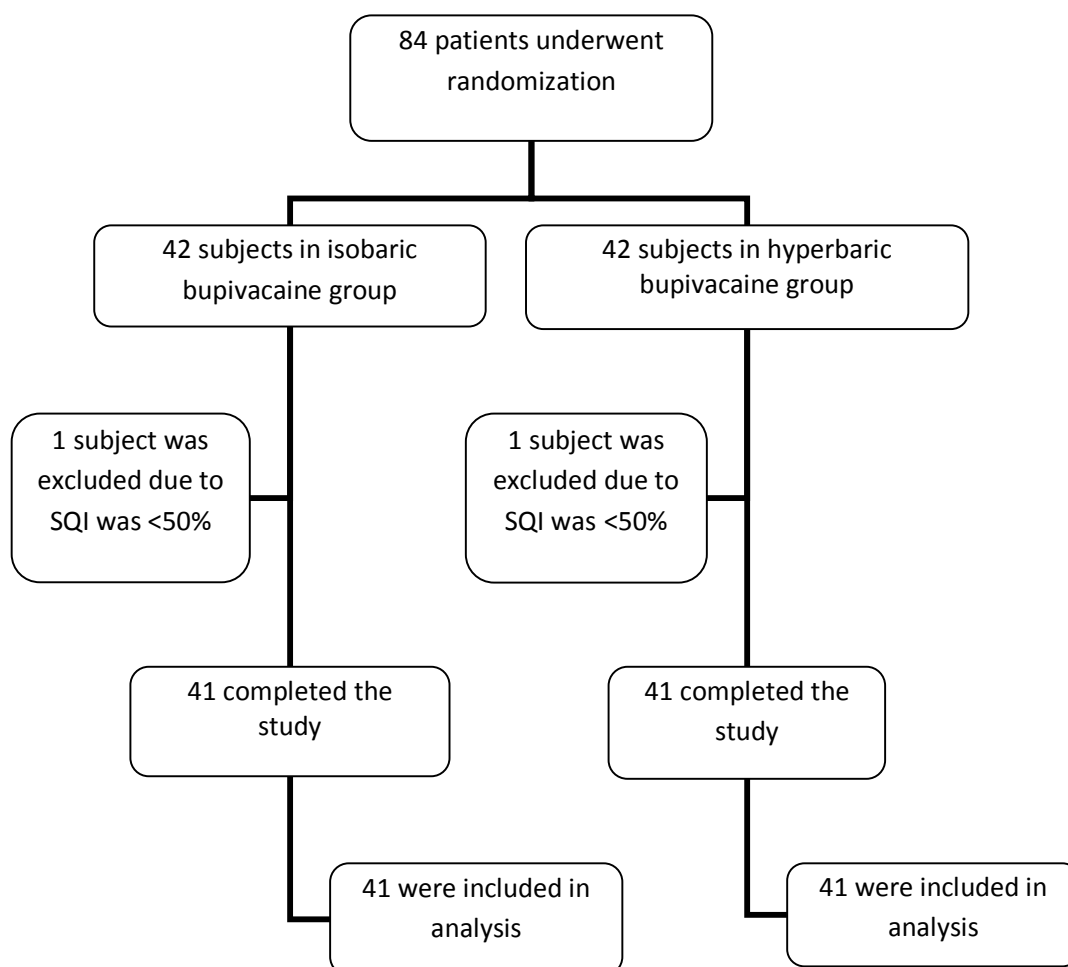
**Table 1. Baseline characteristics and drug consumption of the two groups (mean±SD)**

	Isobaric bupivacaine (n=41)	Hyperbaric bupivacaine (n=41)	p value
Age (year)	28.2 ± 5.7	28.6 ± 5.7	0.77*
BMI (kg/m <sup>2</sup> )	29.4 ± 4.2	27.6 ± 2.8	0.09*
HR (beat /min)	94 ± 13.6	98 ± 15.3	0.14**
MAP (mmHg)	88.1 ± 23.8	86.8 ± 15.8	0.24**
Tympanic T (°C)	36.5 ± 0.1	36.7 ± 0.2	0.37**
Axillary T (°C)	37.11 ± 0.1	37 ± 0.45	0.14**
SQI	73 ± 14.6	87.4 ± 14.2	0.24**
EMG (%)	99.9 ± 0.4	96.9 ± 14.6	0.19**
ASA (I/II)	35/6	34/7	0.25**
Height (cm)	161 ± 8	160 ± 9	0.51*
Duration of surgery (min)	45 ± 11	43 ± 13	0.31**
Ephedrine consumption (mg)	3.3 ± 0.4	3.6 ± 0.5	0.41*
Atropine consumption (mg)	0.3 ± 0.01	0.25 ± 0.02	0.11*

HR, heart rate; MAP, mean arterial pressure; SQI, signal quality index; EMG, electromyography; T, temperature; BMI, body mass index

\*Independent t-test

\*\* Mann-Whitney test



**Figure 1.** Flow diagram of enrolled study patients

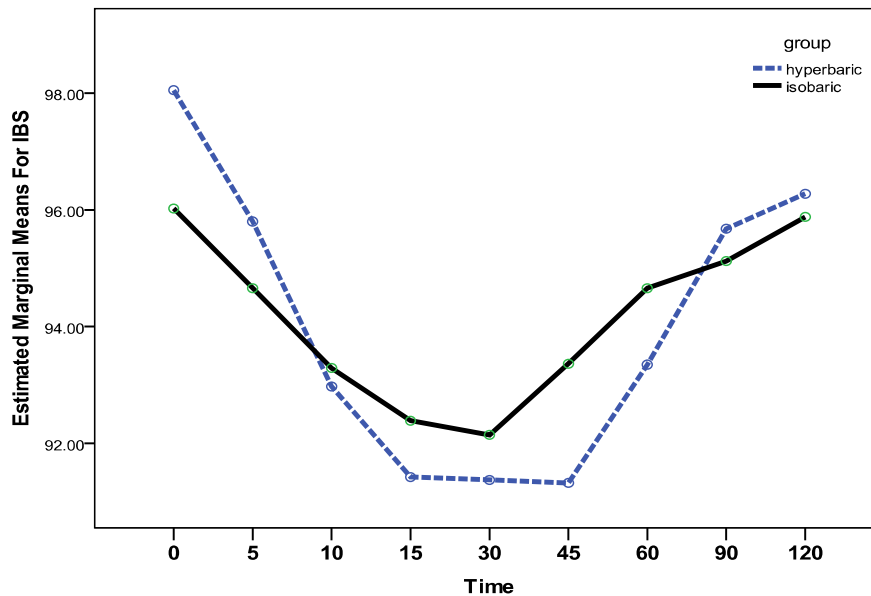
**Table 2. Bispectral index during cesarean section (mean±SD)**

time	Hyperbaric bupivacaine	Isobaric bupivacaine	p value**
baseline	98 ± 2.7	96 ± 3.3	0.25
5 min	95.8 ± 3.8	94.7 ± 3.4	0.76
10 min	93 ± 6.2	93.3 ± 4.3	0.66
15 min	91.4 ± 6.3	92.4 ± 5	0.37
30 min	91.4 ± 4.5	92.1 ± 5.5	0.39
45 min	91.3 ± 3.9	94.7 ± 4	0.08*
60 min	93.4 ± 3.9	94.7 ± 4	0.16
90 min	95.7 ± 2.6	95.1 ± 2.6	0.38
120 min	96.3 ± 2.3	95.9 ± 2.7	0.48
p value***	0.021		

\* Statistically Significant

\*\* Mann-Whitney test

\*\*\* Repeated measurement ANOVA between subjects



**Figure 2.** Changing trend of BIS values during spinal anesthesia

## DISCUSSION

Isobaric and hyperbaric bupivacaine are widely used drugs for spinal anesthesia. The effect of these drugs on BIS score has been investigated but the comparison of these two kinds of drugs has not been done until now.<sup>7,8</sup> Based on our results, the BIS score of patients undergoing intrathecal spinal anesthesia with hyperbaric or isobaric bupivacaine was not significantly different. BIS change after 45 minutes from baseline was the only significant difference between two groups. Several theories have been proposed to explain the sedative effects of spinal anesthesia, including a direct effect of the local anesthetic, either by systemic absorption or rostral spread through the CSF, attenuating stimulation of the reticular activating system in a

situation where there is also decreased afferent input. Pollock et al. reported that the greatest variations from baseline BIS values in non sedated patients occurred at 30 and 70 minutes after induction of spinal anesthesia, and suggested that delayed rostral spread of local anesthetics might be responsible.<sup>17</sup> A previous study<sup>18</sup> in which ‘high’ and ‘low’ blocks (medians T3 vs. T10) were produced by the injection of different doses of hyperbaric bupivacaine (17.5 vs. 7.5 mg), reported that the BIS values did not change until 20 minutes after induction of spinal anesthesia, the propofol infusion having been started, after 15 min in both groups. The authors suggested that 15–20 minutes was not long enough for local anesthetics to spread rostrally in concentrations sufficient to influence the electrical activity of higher neuronal centres.<sup>18</sup> Although the possibility of rostral

spread of the intrathecal local anesthetics cannot be excluded, there is a low probability of this occurring, particularly in the 'low' block groups. The results of the present study supported these conclusions.<sup>8</sup>

Marucci et al.<sup>3</sup> reported that in pregnant women undergoing cesarean delivery using spinal anesthesia, 12.75 mg hyperbaric bupivacaine 0.5% with fentanyl had more sedative effect than the same dose of this drug without fentanyl which resulted in the increased anesthetic block density. In the group that had only received bupivacaine, the peak sedative effect was seen 35-45 minutes after injection, while women who had bupivacaine plus fentanyl the peak sedative effect was seen at 45-70 minutes. Therefore, it was concluded that spinal anesthesia in cesarean is in association with loss of consciousness especially if two drugs are used simultaneously. Intrathecal spinal anesthesia has anti anxiety effect in addition to spinal ganglion blockade and decrease afferent signals from the spinal cord.<sup>3</sup> More recent data have suggested that the reduced local anesthetic requirements predate the mechanical effects of the gravid uterus. In animal studies, chronically administered progesterone has been found to reduce anesthetic requirements. In addition, it has been suggested that the increased concentrations of endorphins and dynorphins found in pregnant rats may be related to altered pain threshold. This evidence suggests a multi factorial explanation for the decreased anesthetic requirement.<sup>2,19</sup>

In another study,<sup>6</sup> 46 pregnant women were divided into five groups that received 2.5 ml bupivacaine isobar 0.5% and 20 micrograms fentanyl intrathecal in group I, 2.5 ml bupivacaine isobar 0.5% intrathecal and 100 micrograms fentanyl intravenous in group II, 2.5 ml bupivacaine isobar 0.5% intrathecal and 100 micrograms of epidural fentanyl in group III, 2.5 ml bupivacaine isobar 0.5% intrathecal in group IV and finally 3 ml bupivacaine isobar 0.5% intrathecal for group V. BIS values of the group administered intrathecal fentanyl were lower than those of other groups. In addition, the time in which the BIS score was 80 or less was more than other groups.<sup>6</sup> Therefore, the BIS value was significantly decreased only by intrathecal fentanyl for cesarean section.<sup>6</sup>

In addition to combination of drugs, baricity is another known factor that affects consciousness in spinal anesthesia.<sup>8,10</sup> No study has compared the effect of hyperbaric and isobaric bupivacaine on the BIS score. According to the present study, the BIS scores during surgery began to reduce after intrathecal injection in both of these drugs. Moreover, the trend of BIS scores was lower in hyperbaric bupivacaine group than the other. However, it was not statistically significant. One study<sup>8</sup> examined the effect of different levels of spinal anesthesia for varicose vein surgery, induced by solutions of different baricity but containing the same amount of local anesthetic agent, on the requirement for sedation with propofol. The known difference in level of spinal

anesthetic block induced by solutions of different baricity but the same dose of local anesthetic was associated with different requirements for propofol sedation as determined by BIS assessment. The maximum levels of block in the control hyperbaric and isobaric groups were T4 (T3-T9) and T10 (T8-T11). Cumulative consumption of propofol to maintain the BIS value was also less in the hyperbaric than in the isobaric group that was influenced by the block height, not the dose of local anesthetic. However, this study did not demonstrate a correlation between block level and propofol requirement, because the block levels were not so diverse.<sup>8</sup>

Conversely, another study investigated whether the specific gravity of bupivacaine combined with intrathecal fentanyl in spinal anesthesia for cesarean section effected the BIS values.<sup>10</sup> Thirty one parturients scheduled for cesarean section were allocated into two groups: 0.5% isobaric bupivacaine 2 ml plus fentanyl 20 microgram (I group, n = 14) or 0.5% hyperbaric bupivacaine 2 ml plus fentanyl 20 microgram (H group, n = 17). BIS values were recorded throughout the anesthesia. The lowest BIS values in the I group and in the H group were  $77 \pm 13$  and  $87 \pm 6$ , respectively. The cumulative time for BIS values below 80 in the I group was longer than that in the H group. The number of BIS decreased cases, defined as the cases in which the BIS values continuously fell down to or below 80 for more than 10 minutes, was higher in the I group than in the H group. The BIS values in patients who received intrathecal isobaric bupivacaine with fentanyl were lower than those with intrathecal hyperbaric bupivacaine and fentanyl.<sup>10</sup>

In our study, there was no difference about ephedrine consumption during evaluation. Yentis et al.<sup>19</sup> found that ephedrine but not phenylephrine, increases bispectral index values during combined general and epidural anesthesia. There were two limitations in our study. First, the plasma concentrations of local anesthetics were not measured. Second, there was no control group, where intrathecal local anesthetic was not given.

In conclusion, in pregnant women undergoing elective cesarean section using spinal anesthesia, the BIS during surgery began to reduce when the patients were injected by both of hyperbaric or isobaric bupivacaine and these drugs did not have different effects on the BIS until 2 hours after induction of spinal anesthesia.

## CONCLUSION

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