 DOI: 10.18231/2394-4994.2017.0060

Combination of buprenorphine with hyperbaric bupivacaine administered either as a mixture or sequentially for spinal anaesthesia for caesarean section

Archana Shivashankar[1,*], Prapti Rath[2], Sadashivan S. Iyer[3], CVR Mohan[4]

[1,2,3]Assistant Professor, [4]HOD, Dept. of Anaesthesiology, M.S, Ramaiah Medical College & Hospital, Bangalore

***Corresponding Author:**
Email: archvinddoc@yahoo.co.in

Abstract

Introduction: Density of local anesthetic is an important determining factor for the distribution, duration and degree of the block achieved in spinal anaesthesia, with small changes influencing its distribution. Mixing of opiods with hyperbaric bupivacaine in the same syringe for injecting into subarachnoid space is a routine practice, which can change the density of both drugs thus affecting their spread.

Our study aims to compare the efficacy of premixed or sequential injections of bupivacaine and buprenorphine for spinal anaesthesia for caesarean section in terms of block characteristics and haemodynamics.

Materials and Method: 120 parturients undergoing elective caesarean section were randomly allocated to two groups, Group M received spinal anaesthesia with 10 mg of 0.5% hyperbaric bupivacaine mixed with 90 micrograms of buprenorphine in a single syringe. Group S received 0.5% hyperbaric bupivacaine 10mg followed by 90 micrograms of buprenorphine through separate syringes.

Results: There was significant difference in the highest level of sensory block to pin prick in Group M compared to Group S (T5 vs T6) ($P < 0.0001$). 20% patients had sensory level of T1 in Group M where as none of the patients in Group S had sensory level T1. Hypotension was noted in 58.3% of patients in Group S and 21.7% in Group M. The total mean dose of vasopressor used in Group M was 5.75+/- 5.85 and 1.85+/- 4.03 in Group S ($P < 0.0001$).

Conclusion: Mixing of Buprenorphine with hyperbaric bupivacaine is associated with greater incidence of hypotension which necessitates the use of larger doses of vasopressor intraoperatively, which could be due to higher level of sensory blockade.

Keywords: Spinal anaesthesia, Caesarean section, Buprenorphine, Bupivacaine, Premixed, Sequential.

Received: 14th December, 2016 **Accepted:** 20th March, 2017

Introduction

There has been an escalation in the number of caesarean sections done in the last twenty years in the developed as well as in the developing countries, most probable reason being comfort of the patients and preference of the obstetricians.(1) Because of increased risks associated with general anaesthesia in pregnant women, there is greater tendency towards neuraxial anaesthesia in caesarean section.(2)

Spinal anaesthesia with administration of 0.5% Bupivacaine(H) combined with adjuvant have become the method of choice for caesarean section. Intrathecal adjuvants provide a better quality of blockade and extend the duration of analgesia. Furthermore, addition of adjuvants allows, reducing the dose of bupivacaine minimizing the haemodynamic effects.(3) Opiods are widely used for intrathecal administration and benefits of neuraxial narcotics over systemic narcotics are well established.(4) Buprenorphine is a mixed agonist-antagonist opiod with superior affinity at both Mu and kappa receptors. It is as efficacious as morphine in providing analgesia in all clinical conditions. When injected intrathecally, buprenorphine is compatible with CSF and does not cause adverse reactions.(5,6)

Hyperbaric bupivacaine injected into the subarachnoid space for caesarean section in the sitting position produces a more predictable block, decreased incidence of hypotension and requires lower doses of vasopressor compared to plaine bupivacaine.(7) The ability to predict the ultimate level of block during spinal anaesthesia is essential in providing adequate anaesthesia while minimizing side effects. Many factors have been identified to regulate the spread of local anaesthetic solutions within the subarachnoid space, which includes patient characteristics, physical properties of CSF, injection technique and dose and properties of the local anaesthetic used.(8,9)

Density is the most important determinant of the distribution, duration and degree of the spinal block achieved. Small changes in the anaesthetic density may influence local anaesthetic distribution both experimentally and clinically.(9,10) Opiod densities are lower than hyperbaric and in some cases, isobaric local anaesthetic. Mixing of opiods with local anaesthetics will decrease the final density of the mixture.(11-13)

It is a routine practice to mix opiods with hyperbaric bupivacaine in a single syringe before injecting the premixed solution into the subarachnoid space, thus altering the density of both the drugs and directing their spread in the subarachnoid space.

The aim of our study was to compare the efficacy of buprenorphine with hyperbaric bupivacaine administered either as a mixture or sequentially for spinal anaesthesia for caesarean section in terms of

block characteristics, maternal haemodynamics, neonatal outcome and post operative pain.

Materials and Method

Institutional Ethics Committee (Regno. ECR/215/Inst/Kar 2013 dated05/04/2016) approval was obtained and written informed consent was taken from all parturients. 122 parturients with single intrauterine gestation aged between 18-40 years, posted for elective caesarean section were enrolled for this prospective randomized controlled study. Parturients with multiple gestations, hypertensive disorder of pregnancy, gestational diabetes, those having contraindications to subarachnoid block, having history of hypersensitivity to bupivacaine or buprenorphine and those with height less than 150 centimeters were excluded from the study. The patients were allocated to one of the two groups using computer generated random table numbers to receive drugs as a mixture or in a sequential manner.

Group M – patients received a mixture of 2ml of 0.5% bupivacaine and 0.3ml (90microgms) of buprenorphine, prepared in a single syringe.

Group S – patient received 2ml of 0.5% bupivacaine followed by 0.3ml (90microgms) of buprenorphine through a separate syringe.

All patients were kept fasting nil for 6 hours before surgery and were pre-medicated with oral Ranitidine 150mgs and Ondensetron 8mgs at night and repeated in the morning prior to surgery. After shifting to the operating room, a good intravenous access was secured and monitoring devices like ECG, pulse oximetry and NIBP were connected.

All patients were preloaded with 500ml of Ringer's lactate intravenously 15-20 minutes before spinal anaesthesia. Under strict aseptic precautions, subarachnoid block was administered with 25G quincke's needle via midline approach in sitting position in L3-4 or L4-5 space. Drugs were injected over 30 seconds including the time for switching of syringes in the sequential administration and patients were made to lie down supine. A senior anaesthesiologist, who was not aware of the drug given, evaluated the block and other haemodynamic parameters.

Heart rate and blood pressure were monitored every 2 minutes for first 20 minutes and then every 5 minutes subsequently till the end of the surgery. Any episodes of hypotension (systolic BP < 90 mm of Hg or fall in BP by > 20% of baseline values) and bradycardia (HR< 50 beats/min) were noted.

Hypotension was managed with rapid infusion of crystalloids and bolus of ephedrine 6mg IV, if hypotension persisted. Bradycardia was treated with inj.Atropine 20µgm/kg IV.

The onset of sensory block was assessed by loss of pin prick sensation. Dermatomal level was assessed every 2 minutes until stabilized and time taken to reach maximum block height was noted. Also time for regression of the block to T10 dermatome level and time when patient demanded first rescue analgesia was noted. Motor block was assessed by modified Bromage scale.

If any patients complained of discomfort or pain during surgery, it was assessed by visual analogue scale(VAS). Patients who complained of moderate to severe pain (VAS >5) was accounted as spinal failure and was converted to general anaesthesia.

Side effects like nausea, vomiting, dry mouth, respiratory depression (RR < 10/min, Spo2 < 92%) was noted. Newborn's APGAR score was determined by the pediatrician at 1min and 5min. Postoperatively any incidence of bradycardia, hypotension, nausea, vomiting, PDPH and neurological deficit was noted.

Assessment of block characteristics and hemodynamics were the primary outcome and post operative side effects and post operative pain were the secondary outcome measures.

Statistical Analysis: Rationality for sample size was based on the study conducted by Desai et al. which revealed that the mean time taken to reach the sensory loss to cold was 7+/-3 minutes and 9+/-4 minutes for mixed and sequential group respectively. Based on the above findings with the power of 90% and α error of 5% it was estimated that minimum 60 patients need to be recruited in each group.

Data analysis was done with the help of computer using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 19.0 for Windows).

Using this software, range, means and standard deviations were calculated for quantitative variables. Frequencies and percentages were calculated for qualitative variables. Student's unpaired 't' test was used to test the significance of difference between quantitative variables. Yale's and Fisher's chi square tests were used for qualitative variables. A 'p' value less than 0.05 was significant.

Results

A total of 122 parturients were enrolled. One patient from each group were excluded as they did not achieve adequate sensory blockade and was converted to general anaesthesia, hence 60 parturients were considered for analysis. Demographic parameters such as age, height, weight, BMI and ASA status were comparable between the groups (Table 1). All patients had uneventful intraoperative course.

Table 1: Characteristics of cases studied

Variable	Value for		'p'
	M Group	S. Group	
Number of cases studied	60	60	-
Age (yrs)	27.5 + 3.6 yrs	27.8 + 4.0 yrs	0.579 Not Significant
Height (cms)	155.9 + 3.6	156.1 + 3.4	0.815 Not significant
Weight (kgs)	69.6 + 8.5	70.2 + 11.8	0.751 Not significant
BMI	28.6 + 3.6	28.8 + 4.5	0.792 Not significant
ASA 1 2	 28(46.7%) 32 (53.3%)	 24 (40%) 36 (60%)	0.2344 Not significant
LP Level L2-3 L3-4 L4-5	 12 (20%) 47 (78.3%) 1 (1.7%)	 10 (16.7%) 50 (83.3% -	0.3234 Not significant
Baby weight (kgs)	2.8 + 0.44	2.78 + 0.52	0.764 Not significant
Oxytosin dose (u)	14.1 + 4.4	14.3 + 3.1	0.719 Not significant
Apgar 1 minute	6.97 + 0.66	6.93 + 0.31	0.7251 Not significant
Apgar 5 minutes	8.8 + 0.71	8.93 + 0.25	0.172 Not significant

There was significant difference in the highest level of the sensory block to pin prick, median being T5, range T4-T1 in Group M and T6, T6-T2 in Group S (P=0.001). 20% (12) in Group M had sensory level of T1 where as none of the patients in Group S had sensory level of T1. 11.7% (7) in Group M had a sensory level of T2 and 5% (3) in Group S(Table 2). No significant differences were noted in the time taken to achieve the highest level of sensory block in both the groups. Whereas, the time required for regression of the sensory block and motor block was insignificantly lower in Group M compared to Group S (Fig. 1).

Table 2: characteristics of spinal block

Event	M Group		S Group		'p'
	No.	%	No.	%	
Time to reach max. sensory level (min)	7.3	2.5	7.6	2.2	0.48 Not Significant
Maximum sensory block height (T- median)	T4	38.3%	T6	61.7%	<0.0001 significant
Time for Regression to T10(min)	126.0	31.7	139.3	25.4	0.013 Significant
Time for Motor recovery(min)	160.6	26.3	170.8	27.9	0.042 Significant
Time for Rescue analgesia(min)	276.8	32.5	271.7	32.6	0.387 Not Significant

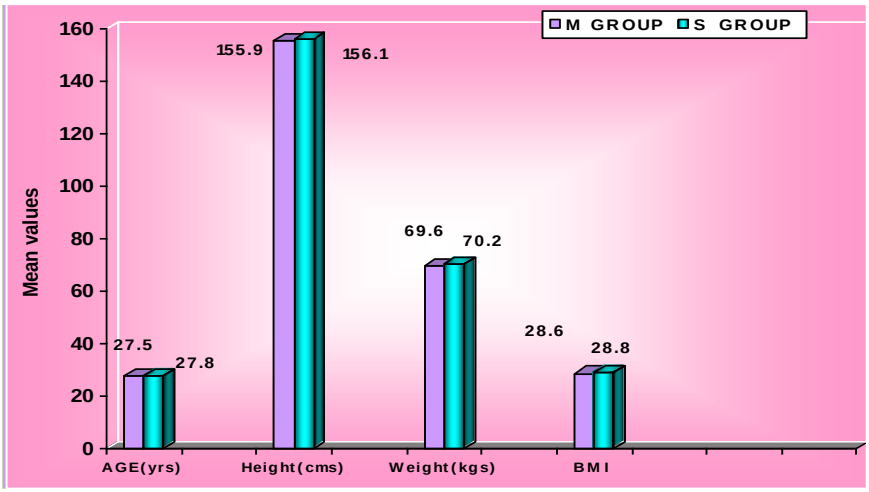

Fig. 1: Demographic data

Hemodynamic parameters showed that there were no significant changes in the heart rate in both the groups, but only one patient in Group M had bradycardia which required treatment with intravenous Inj. Atropine 0.3mg, whereas none of the patients had bradycardia in Group S (Table 3). Hypotension was noted in 58.3% of patients in Group M and 21.7% of patients in Group S which was statistically significant. There was significant fall in systolic and diastolic blood pressure in both the groups at 3,5 and 7 minutes and was more in Group M than Group S (P=0.002) (Fig. 2, 3, 4). The total mean dose of vasopressor used in Group M was 5.75+/- 5.85 and 1.85+/-4.03 in Group S which was significantly higher in sequential group (P< 0.0001).

Table 3: Haemodynamic Data

	Group M	**Group S**	**P**
Frequency of Hypotension (<100 mm of Hg)	35 / 58.3%	13 / 21.7%	<0.0001 Significant
Dose of Ephedrine used (mg) mean	5.75+/-5.85	1.85+/-4.03	<0.0001 Significant
Dose of Atropine used (mg) mean	0.0005	-	-

Table 4: Adverse events

Adverse events	**M Group**		**S Group**	
	No.	**%**	**No.**	**%**
Hypotension	35	58.3	13	21.7
Bradycardia	1	1.7	-	-
Vomiting	1	1.7	-	-
Nausea	-	-	1	1.7
Shivering	5	8.3	1	1.7
Cases with Adverse events	37*	61.7	14*	23.3
Cases without Adverse events	23	38.3	46	76.7
Total	60	100.0	60	100.0
'p'	**<0.0001 Significant**			

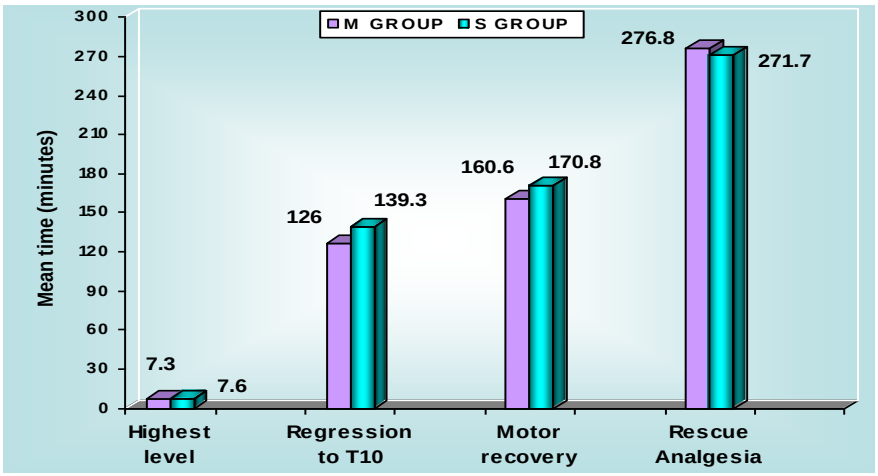

Fig. 2: Time for various events

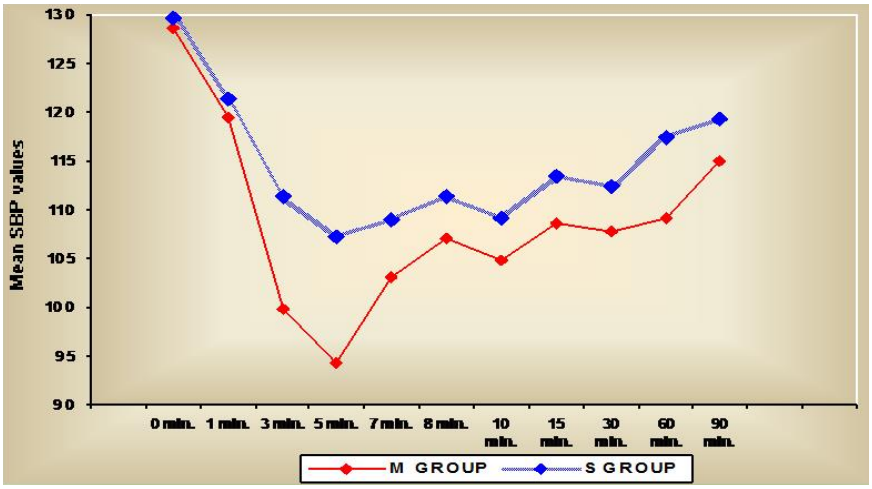

Fig. 3: Changes in systolic blood pressure

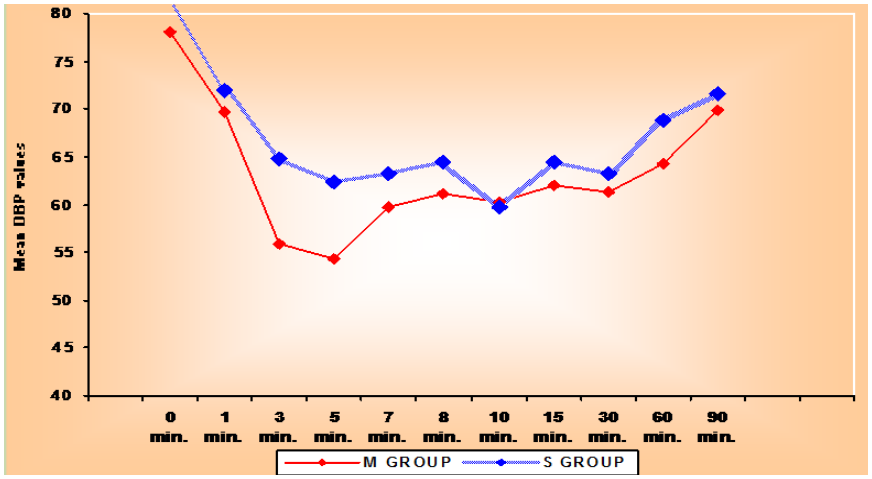

Fig. 4: Changes in diastolic blood pressure

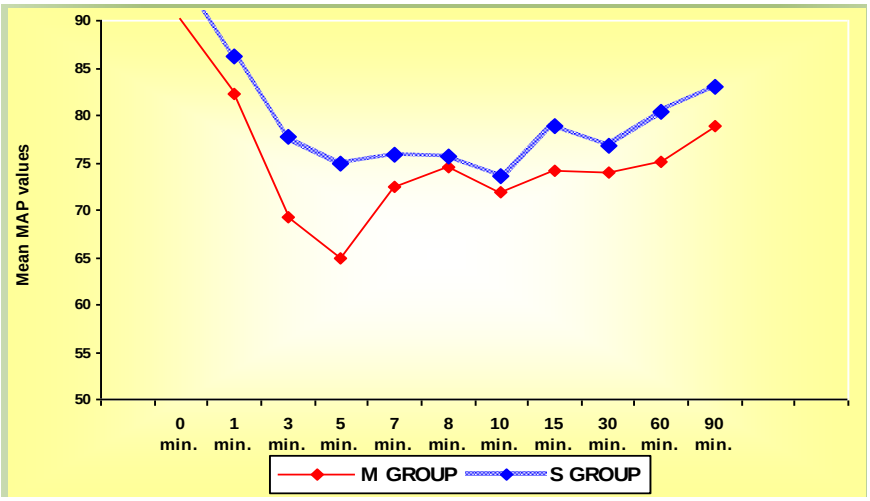

Fig. 5: Changes in mean arterial pressure

Other adverse effects like nausea, vomiting and shivering were comparable in both the groups (Table 4). No respiratory depression or any other complications were recorded in either group.

Discussion

In our study, we found that mixing of buprenorphine with hyperbaric bupivacaine results in a higher level of sensory block and are associated with higher incidence of hypotension requiring larger doses of vasopressor intraoperatively.

The characteristics of block after spinal anaesthesia are affected by factors like position of the patient during and after the injection, physical properties of the CSF, injection technique, dose and density of the drug injected.[14] Richardson et al. in their study indicated that the CSF density is significantly lower in the peripartum period and progesterone may be the physiologic mediator of altered CSF density during pregnancy. They reported that the mean CSF density in term pregnant patient as 1.0003+/- 0.00004 g/dl.[11] The density of 0.5% hyperbaric bupivacaine is 1.023g/dl and that of buprenorphine in 0.9% saline is 0.9990 g/dl.[15] The density of a mixture of buprenorphine and hyperbaric bupivacaine at 37 degrees is 1.018g/dl.[12] In this study we wanted to evaluate whether the intrathecal administration of 0.5% Bupivacaine(H) and buprenorphine through separate syringes have any effect on the block characteristics and haemodynamics parameters.

The density of bupivacaine and patient posture during induction of spinal anaesthesia are believed to be important factors in determining its spread in the CSF. Hallworth et al. in their study have shown that in the lateral position, baricity had no effect on the spread of bupivacaine compared to the sitting position, where there was a statistically significant trend of increasing block height with decreasing baricity.[7] Hare et al. have shown that the density of the anaesthetic mixture decreases in a linear fashion as the fractional volume of anaesthetic is reduced by adding a larger proportion of water or opiod.[16] In this study they demonstrated that addition of opiods to hyperbaric anaesthetics changes the density of the mixture in a predictable manner. This could have important clinical implications since a change in anaesthetic density of 0.0027g/ml has been demonstrated to change the sensory block by about two dermatomes.

There was significant difference in the highest level of sensory block in the mixed group in our study which could be explained due to the fact that mixing of bupivacaine and buprenorphine resulted in alteration of the density of the solution and hence affected its distribution. Desai et al. in their study demonstrated that mixing of fentanyl and morphine with hyperbaric bupivacaine results in a higher level of sensory block than sequential administration. They explained that the reduction in density of bupivacaine by mixing with opiod even if the solution is hyperbaric was responsible for this difference.[17] However, we did not measure the density of the drugs in our study, and we found that patients in mixed group had higher levels of sensory block than those in sequential group.

There was fall in both the systolic and diastolic blood pressure in both the groups in our study, which was significantly lower in the mixed group than the sequential group, and the vasopressor requirement was also higher in Group M. This could be explained on the basis of the fact that the level of the block was higher in the mixed group which resulted in greater sympathetic block and hence a greater fall in the blood pressure. Cesur et al. studied the effect of sequential administration of hyperbaric and plain bupivacaine in parturients, and showed that patients who received the drugs sequentially had lower incidence of hypotension and reduced vasopressor requirement.[18] Keera et al. in their study of two syringe technique for caesarean section also showed lower frequency of hypotension in the sequential group than the mixed group.[19]

It was observed in our study, that patients in whom opiod was mixed with hyperbaric bupivacaine required lesser time for regression of the sensory block and also motor recovery, although the disparity noted is unlikely to be of clinical importance. However, time to rescue analgesia in both the groups were similar. Mixing of buprenorphine with hyperbaric bupivacaine results in change in density of the solution and probably makes the solution less viscous. A less viscous solution would flow more easily through a compressed subarachnoid space, allowing a larger part of the injected dose to reach a higher level.[20]

The limitation of our study is that we did not measure the density of the drugs and also the temperature of the drugs injected as it can affect the spread of the drugs in the CSF. Secondly, we did not investigate whether injecting buprenorphine before bupivacaine has any effects on the block characteristics.

To conclude, mixing of buprenorphine with hyperbaric bupivacaine results in a higher level of sensory block and is associated with higher incidence of hypotension requiring larger doses of vasopressor intraoperatively.

References

1. Yeoh SB, Sng BL, Sia ATH. Anaesthesia for lower-segment caesarean section: Changing perspectives. Indian J Anaesth 2010;54:409-14.
2. J.C. Tortosa, N.S. Parry, F.J. Mercier, J.X. Mazoit, D. Benhamou. Efficacy of augmentation of epidural analgesia for Caesarean Section. Br. J. Anaesth. (2003) 91(4):532-535.
3. Dyer, Robert A, Joubert, Ivan A. Low- dose spinal anaesthesia for caesarean section. Curr Opin Anaesthesiol 2004;17:301-308.
4. Rowlingson, B.A., Genevieve E. Courpas, B.A., Kristin Cheung, M.D., Elaina E. Lin, B.A., Spencer S. Liu, M.D.; Efficacy of Postoperative Patient-controlled and Continuous Infusion Epidural Analgesia versus Intravenous Patient-controlled Analgesia with Opioids: A Meta-analysis. Anaesthesiology 2005;103(5):1079-1088.
5. Dixit S. Post Operative Analgesia after Caesarean Section: An Experience with Intrathecal Buprenorphine. Indian J Anaesth 2007;51(6):515-518.
6. Agarwal K, Agarwal N, Agrawal V, Agrawal A, Sharma M, Agarwal K. Comparative analgesic efficacy of buprenorphine or clonidine with bupivacaine in the caesarean section. Indian J Anaesth 2010;54:453-7.
7. Hallworth SP, Fernando R, Columb M, Stocks GM. The effect of posture and baricity on the spread of intrathecal bupivacaine for elective caesarean delivery. Anesth Analg 2005;100:1159-1165.
8. Greene NM. Distribution of local anaesthetic solutions within the suarachnoid space. Anesth Analg 1985;64:715-30.
9. Stientra R, Gielen M, Kroon JW, Van Poorten F. The influence of temperature and speed of injection on the distribution of a solution containing bupivacaine and methylene blue in a spinal canal model. Reg Anesth 1990;15: 6-11.
10. Bannister J, McClure JH, Wildsmith JAW. Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine. Br J Anaesth 1990;64:232-34.
11. Richardson MG, Wissler RN. Densities of dextrose free intrathecal local anaesthetics, opiods, and combinations measured at 39C. Anesth Analg 1997;84:95-99.
12. Imbelloni LE, Morelre AD, Gaspar FC, Gouvela MA, Cordelro JA. Assessment of densities of local anaesthetics and their combination with adjuvants. An Experimental study. Rev Bras Anaesthesiol 2009;59:154-65.
13. Parlow JL, Money P, Chan P, Raymond J, Milne B. Addition of opiodsalters the density and spread of intrathecal local anaesthetics? An invitro study. Can J Anesth 1999;15:6-11.
14. Uma S, A Kumar, Gandhi, Saxena, Dutta, Chandra, Singh. Hyperbaric or plain bupivacaine combined with fentanyl for spinal anaesthesia during caesarean delivery. Indian J Anaesth 2004;48(1):44-46.
15. ME Nicol, A Holdcroft. Density of intrathecal agents. Br J Anaesth 1992;68:60-63.
16. Hare GMT, Ngan JCS. Density determination of local anaestheticopiod mixtures for spinal anaesthesia. Can J Anaesth 1998;45:341-346.
17. Desai S, Lim Y, Tan CH, Sia AT. A randomized controlled trial of hyperbaric bupivacaine with opiods, injected as either a mixture or sequentially, for spinal anaesthesia for caesarean section. Anaesth Intensive Care. 2010;38:280-84.
18. Cesur M, Alici HA, Erdem AF, Borekci B, Silbir F. Spinal anaesthesia with sequential administration of plain and hyperbaric bupivacaine provides satisfactory analgesia with haemodynamic stability in caesarean section. Int J ObstetAnesth 2008;17:217-22.
19. Keera AA, Elnabtity AM. Two syringe spinal anaesthesia technique for caesarean section: A controlled randomized study of a simple way to achieve more satisfactory block and less hypotension. Anesth Essays Res 2016;10:312-18.
20. C Connolly, GA McLeod, JAW Wildsmith. Spinal anaesthesia for caesarean section with bupivacaine 5 mg/ml in glucose 8 or 80 mg/ml. Br J Anaesth 2001;86(6):805-7.