



ORIGINAL ARTICLE

Comparing the Conventional with Low Dose of Bupivacaine Plus Fentanyl in Spinal Anesthesia on the Neonate Apgar Score in Yazd City

Running Title: Bupivacaine Plus Fentanyl in Spinal Anesthesia

Masoud Khoshbin¹, Ahmad Shajari¹, Golzar Sharifian^{2*}

¹Aliebne-Abitaleb School of Medicine, Islamic Azad University, Yazd Branch, Yazd, Iran

²Young Researchers and Elites Club, Faculty of Medicine, Islamic Azad University, Yazd branch, Yazd, Iran

* Corresponding Author: Golzar Sharifian, E-mail: Sharifiangolzar@gmail.com

ARTICLE INFO

Article history Received:
Aug 06, 2020
Accepted: Aug 08, 2020
Published: Aug 25, 2020
Volume: 5
Issue: 2

Key words:
Cesarean Section,
Spinal Anesthesia,
Bupivacaine,
Fentanyl,
Apgar

ABSTRACT

Introduction: Spinal anesthesia is the preferred method of anesthesia in cesarean section, due to less complications. The augmentation of opioids to spinal anesthetics can improve the quality and increase the duration of analgesia. This study aimed to compare the conventional with low dose of bupivacaine plus fentanyl in spinal anesthesia on the neonate Apgar score in elective cesarean section. **Methods:** The present double-blind randomized clinical trial was conducted on 150 pregnant mothers undergoing cesarean section with the spinal anesthesia during 2017-2018. The mothers were randomly assigned to two groups of 75. The spinal anesthesia was performed in the first group with the injection of 15 mg of 0.5% hyperbaric bupivacaine plus 1 ml of normal saline, and in the second group with the injection of 12.5 mg of 0.5% hyperbaric bupivacaine plus 25 µg of fentanyl. For both groups, 1- and 5-minute neonatal Apgar scores were assessed. Finally, the data were analyzed by SPSS17 software using statistical tests. **Results:** The mean age of the samples was 30.1±5.19 years with a range of 18-42 years (P-value=0.246). The mean gestational age was 38 weeks, the mean 1-minute Apgar score was 8.88 and the mean 5-minute Apgar score was 9.89 **Conclusion:** With the augmentation of fentanyl to bupivacaine for spinal anesthesia, the conventional dose can be reduced, which not only reduces the common side effects of Marcaine, but also provides an appropriate level of anesthesia and does not affect the neonatal Apgar score.

INTRODUCTION

The cesarean section is a common termination of pregnancy that is expanding with the advancement of medical knowledge. With electronic fetal monitoring, cesarean section is used today for birth at older ages and in breech birth. In the cesarean section, the spinal anesthesia is a conventional anesthetic method, and it seems more appropriate than general anesthesia as it facilitates the relationship between mother and baby and the onset of early infant feeding (1). The spinal anesthesia is a subcategory of regional anesthesia, performed by injection of a local anesthetic solution in the subarachnoid space (intrathecal) (2). The specific sensory block level is applied in each surgery, depending on the process. For example, T4-T6 levels (spinal cord 4 to 6) are appropriate for cesarean section. Upper sensory block level causes hypotension. Hypotension, need for ephedrine and nausea are some of the complications that occur when using high doses of spinal anesthetics, such as bupivacaine, hereby resulting in longer recovery time (3). Anesthesiologists face a variety of complications for cesare-

an section, most notably the side effects of using anesthetics on the fetus. The anesthetics after crossing the placenta, have various effects, such as weakening of the central nervous system (CNS) and respiratory distress on the fetus. Each of these complications can cause other abnormalities and ultimately death of the baby (4). Given the complications noted, attempts have been made to exclude, as far as possible, debilitating CNS drugs such as narcotics or benzodiazepines for cesarean section. However, failure to prescribe these medications may also have other serious consequences for the mother (5). For this reason, today it has been tried to minimize the risk of harmful birth of healthy babies by producing new drugs with short half-life, even for several minutes in some cases. Moreover, the mother will experience a painless delivery (6). Therefore, the use of intrathecal drugs along with local anesthetics and its effect has been evaluating on the level of anesthesia and analgesia and the duration of anesthesia. The use of narcotics combined with local anesthetics in the spinal anesthesia increases the duration of anesthesia, enhances the severity of anesthesia and analgesia,

and reduces the dose required by the anesthetics (7). Hyperbaric bupivacaine is a topical anesthetic that is commonly used in spinal anesthesia for cesarean section. However, in most cases, drugs are co-administered to prolong and exacerbate the effect of bupivacaine (8). The bupivacaine 0.75% with the glucose 8.25% is one of these drugs available to produce hyperbaric type. Recommended dose is 5-20 mg and duration of effect is 90-120 minutes for the bupivacaine. The bupivacaine has a strong sensory block (lower incidence of tourniquet pain), but weaker than the motor block. There are limitations in the use of this medication as well. The augmentation of vasoconstrictors is accompanied by a significant increase in the prevalence of neurological symptoms (9). Fentanyl is a short-acting opioid drug that appears to have no cumulative effects and delayed apnea of other narcotics due to its short duration of effect. It also metabolizes rapidly into the body of the baby, despite the rapid passage through the placenta in the body of the fetus, and thus has less adverse effects on the fetus (10). The rapid metabolism of Fentanyl causes its plasma concentration to decrease rapidly after discontinuation of infusion. The clearance of this drug is several times higher than the liver blood flow, which is consistent with the large extra-hepatic metabolism (10). Therefore, the present study used this drug with a major anesthetic. The Apgar score system should be employed to measure the effect of this association. The Apgar score is a scoring system developed by Virginia Apgar in 1953 and is clinically a useful tool for identifying newborns requiring resuscitation and determining the effectiveness of any action for resuscitation (11). Accordingly, it seems necessary to assess the risks and benefits of opiate augmentation to local anesthetic in cesarean section and its effect on neonatal Apgar score. This study aimed to compare the conventional with low dose of bupivacaine plus fentanyl in spinal anesthesia on the neonate Apgar score in elective cesarean section.

MATERIALS AND METHODS

The present clinical trial with parallel design was carried out after receiving the approval of the Ethics Committee of Azad Islamic University of Yazd (Yazd, Iran) and obtaining informed written consent on 150 volunteers undergoing cesarean section with spinal anesthesia. The injection process of anesthetics was explained for patients. Information about spinal anesthesia was provided to pregnant mothers by brochures and specialist. Inclusion criteria were healthy conditions for volunteers undergoing cesarean section. Exclusion criteria were a history of chronic disease or mental and physical disability, and a high risk of vulnerability for study diagnosed by a gynecologist.

Finally, 150 pregnant women referred to the Shohada-ye Kargar Hospital in Yazd (Yazd, Iran) were selected for study. The pregnant women were randomly assigned to two groups of 75. Their medical information was extracted from the records by maintaining the confidentiality of the identity information. All mothers received a liter of ringer serum before the spinal anesthesia, and then an anesthesiologist injected the spinal anesthetic in L3-L4 space with a 25-gauge needle in a sitting position. The spinal anesthesia was performed in the first (placebo) group with the injection of 15 mg of

0.5% hyperbaric bupivacaine plus 1 ml of normal saline, and in the second group with the injection of 12.5 mg of 0.5% hyperbaric bupivacaine plus 25 µg of fentanyl in the interarticular space. For both groups, 1- and 5-minute neonatal Apgar scores were assessed and the complications such as vomiting and shivering were evaluated.

Data were collected in a pre-prepared questionnaire. Finally, the obtained data were analyzed by SPSS17 software using t-test and chi-square test. P-value ≤ 0.05 was considered to be significance level.

RESULTS

According to Table 1A, 40% of the group under the spinal anesthesia by bupivacaine was under the age of 30 years, and 53% of the group under the spinal anesthesia by bupivacaine + fentanyl was under the age of 30 years. This association was tested by means of chi-square test, which was not significant (P-value=0.102); therefore, the age of mothers was considered as homogeneous between the two groups of study. With regard to homogeneity of age, the frequency distribution of their neonatal gender was also examined.

In accordance with Table 1B, 53.3% of the group under the spinal anesthesia by bupivacaine had baby girl and 38.7% of the group under spinal anesthesia by bupivacaine + fentanyl had baby girl. This association was tested by chi-square test, which was not significant (P-value=0.072), meaning no association was found between the sex of the baby and the randomized grouping of mothers in this study. Finally, it was shown that there is no significant difference between the two groups in maternal age and neonatal sex in the study (Table1). According to Table 2A, vomiting was reported in 46.7% of the group under the spinal anesthesia by bupivacaine and in 20.3% of the group under the spinal anesthesia by bupivacaine + fentanyl. This association was tested by chi-square test, which was significant (P-value=0.029), which means more vomiting was reported by c-section volunteers in the group under spinal anesthesia by bupivacaine.

In accordance with Table 2B, the shivering was reported in 65.3% of the group under the spinal anesthesia by bupivacaine and 37.3% of the group under the spinal anesthesia by bupivacaine + fentanyl. This association was tested by chi-square test, which was significant (P-value=0.001), that is, the pregnant mothers had more shivering in the group under spinal anesthesia by bupivacaine (Table2).

According to Table 3A, the mean 1-minute Apgar score was 8.93 ± 0.703 with a range of 8 to 10 in the group under the spinal anesthesia by bupivacaine, and 8.82 ± 0.723 with the range of 8 to 10 in the group under spinal anesthesia by bupivacaine + fentanyl. This difference was tested by t-test, which was not significant (P-value=362), i.e. the two groups reported the same results in the 1-minute Apgar score.

According to Table 3B, the mean 5-minute Apgar score was 9.93 ± 0.251 with a range of 9 to 10 in the group under spinal anesthesia by bupivacaine and 9.85 ± 0.356 with the range of 9 to 10 in the group under spinal anesthesia by bupivacaine + fentanyl. This difference was evaluated by t-test, which was not significant (P-value=0.114), which means that the two groups showed the same results in the 5-minute Apgar score (Table3).

Table 1. Frequency distribution of maternal age and neonatal sex in the two groups of intervention and placebo

A) Frequency distribution of maternal age in both groups							
Group	Bupivacaine		Bupivacaine + Fentanyl		Total		p-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
Maternal age							
18-29	30	40	40	53.3	70	46.7	0.102
30-42	45	60	35	46.7	80	53.3	
Total	75	100	75	100	150	100	
B) Frequency distribution of neonatal sex in both groups							
18-29	40	53.3	29	38.7	69	46	0.072
30-42	35	46.7	46	61.3	81	54	
Total	75	100	75	100	150	100	

Table 2. Relative frequency of vomiting and shivering in the study volunteers

A) Relative distribution of vomiting in both groups							
Group	Bupivacaine		Bupivacaine + Fentanyl		Total		p-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
Vomiting incidence							
Yes	35	46.7	22	29.3	57	38	0.029
No	40	53.3	53	70.7	93	62	
Total	75	100	75	100	150	100	
B) Frequency distribution of shivering in both groups							
Yes	49	65.3	28	37.3	77	51.3	0.001
No	26	34.7	47	62.7	73	48.7	
Total	75	100	75	100	150	100	

According to Table 4A, in mothers under the age of 30 years, the mean 1-minute Apgar score was 8.80 ± 0.664 with a range of 8 to 10 in the group under the spinal anesthesia by bupivacaine, and 8.85 ± 0.662 with a range of 8 to 10 in the group under spinal anesthesia by bupivacaine + fentanyl. This difference was tested by t-test, which was not significant (P -value=0.756). In the mothers over the age of 30 years, the mean 1-minute Apgar score was 9.02 ± 0.722 with a range of 9 to 10 in the group under spinal anesthesia by bupivacaine, and 8.80 ± 0.797 with a range of 9 to 10 in the group under spinal anesthesia by bupivacaine + fentanyl. This difference was

tested by t-test, which was not significant (P -value=0.196). Therefore, maternal age is not effective in the association between the type of anesthetic and the 1-minute Apgar score, and the 1-minute Apgar score is the same in each age group of mothers.

According to Table 4B, in the mothers under the age of 30 years, the mean 5-minute apgar score was 9.93 ± 0.253 with a range of 9 to 10 in the group under the spinal anesthesia by bupivacaine and 9.85 ± 0.361 with a range of 9 to 10 in the group under spinal anesthesia by bupivacaine + fentanyl. This difference was tested by t-test, which was not significant

Table 3. The mean 1- and 5-minute Apgar scores in the study groups

A) the mean 1-minute Apgar score in both groups						
Groups	Frequency	Mean	Standard deviation	Minimum	Maximum	<i>P</i> -value
Bupivacaine	75	8.93	0.703	8	10	0.362
Bupivacaine + Fentanyl	75	8.82	0.723	8	10	
Total	150	8.80	0.713	8	10	
B) the mean 5-minute Apgar score in both groups						
Bupivacaine	75	9.93	0.251	9	10	0.114
Bupivacaine + Fentanyl	75	9.85	0.356	9	10	
Total	150	9.89	0.309	9	10	

Table 4. The mean 1- and 5-minute Apgar scores in terms of age

A) the mean 1-minute Apgar score in both groups in terms of maternal age							
Maternal age	Groups	Frequency	Mean	Standard deviation	Minimum	Maximum	<i>P</i> -value
18-29	Bupivacaine	30	8.80	0.664	8	10	0.756
	Bupivacaine + Fentanyl	40	8.85	0.662	8	10	
	Total	70	8.82	0.658	8	10	
30-42	Bupivacaine	45	9.02	0.722	8	10	0.196
	Bupivacaine + Fentanyl	35	8.80	0.797	8	10	
	Total	80	8.92	0.759	8	10	
B) the mean 5-minute Apgar score in both groups in terms of maternal age							
18-29	Bupivacaine	30	9.93	0.253	9	10	0.285
	Bupivacaine + Fentanyl	40	9.85	0.361	9	10	
	Total	70	9.88	0.320	9	10	
30-42	Bupivacaine	45	9.93	0.252	9	10	0.265
	Bupivacaine + Fentanyl	35	9.85	0.355	9	10	
	Total	80	9.90	0.301	9	10	

(P -value=0.285). In the mothers over the age of 30 years, the mean 5-minute Apgar score was 9.93 ± 0.252 with a range of 9 to 10 in the group under the spinal anesthesia by bupivacaine and 9.85 ± 0.355 in the range of 9 to 10 in the group under spinal anesthesia by bupivacaine + fentanyl. This difference was tested by t -test, which was not significant (P -value=0.265). Therefore, maternal age is ineffective in the association between the type of anesthetic and the 5-minute Apgar score, and the 5-minute Apgar score is the same in each age group of mothers (Table 4).

DISCUSSION

Fifty years ago, Brock presented the first modern depiction of HCM according hemodynamic at cardiac catheterization or operation in 1957 (3). In 1958 Teare described the same case from the autopsy laboratory (4).

According to the echocardiographic reference books the treatments which offered for HCM is varied, from medical treatments such as beta-blockers and calcium channel blockers to surgical choices such as surgical myotomy, myectomy or alcohol ablation of septum. The mechanism of surgical treatment defers to lightening hemodynamic deviances involving MR and outflow tract obstruction. Successful procedure outcomes were acute and effective attenuation of the proximal septum and relieving the notable outflow obstruction or mitral regurgitation. The alternative HCM treatment would be dual-chamber pacing, employing to improve abnormal short diastolic filling period (5, 6).

Septal myectomy indications including; resistance to appropriate medical therapy such as β -adrenergic and calcium channel blocker, pacemaker therapy, septal ablation, as well as, high LV outflow gradient at rest position (usually greater than 50 mmHg). Another indication for surgical myectomy is trivial or distant gradients at rest which increase (more than 50 mmHg) by exercise (isoproterenol), after an ectopic beat, or ending the exercise phase. Episode of atrial fibrillation is considered as another indication of surgical myectomy. Consequently, patients with limited symptoms but severe increased LVOT gradients especially if there is considerable simultaneous mitral regurgitation or history of faint or obscure cardiac arrest and young-age patients who had experienced gradient elevation more than 100 mmHg are candidate for operation. As a result, coronary artery bypass grafting (CABG) alone doesn't alleviate symptoms in patients with HCM and coronary artery disease, so in HCM patients who also, suffer from coronary artery disease both CABG and septal myectomy are advisable (7).

To the best of our knowledge, there was no data about non-obstructive HCM patients who get candidate for simultaneously valve repair and CABG surgery. In Dimitrow et al. study 37 non-obstructive HCM patients were studied. The mean value of septal wall thickness in these patients were 23.3 ± 4.1 mm. Patients were on medical treatment with verapamil or beta blockers. They aimed to improve the diagnosis of obstruction by inducible gradient through exercise, even in patients without obstruction in supine resting position. In these patients LVOT gradient at rest and in supine position was less than 30 mmHg. Eight patients showed upright position related gradient increment for more than 30 mm. In remained 10 patients,

significant LVOT gradient increase were measured at peak of the exercise (1).

Our study presents a patient with post exercise LVOT gradient increment who undertook Mitral valve replacement (MVR) and CABG and septal myectomy simultaneously. His post exercise LVOT gradient had borderline elevation, then septal myectomy considered the best choice accompanied by CABG and MVR.

The LVOT gradient threshold for implementation of major invasive interventions, such as septal myectomy is about 50 mmHg. As Mingo et al. study shows, one of the most important independent predictive factors in mortality of hypertrophic cardiomyopathy is outflow tract obstruction. Other predictive factors that had been mentioned in this study were atrial fibrillation, restricted functional capacity (NYHA class II, III or IV) and the ultimate left ventricular wall thickness was at least 30 mm (8).

CONCLUSION

The augmentation of fentanyl to hyperbaric bupivacaine in spite of developing a suitable neuraxial blockade has no effect on neonatal Apgar score. According to the present study, the augmentation of fentanyl and the administration of low-dose bupivacaine cause less complications (vomiting and shivering).

ACKNOWLEDGMENTS

We thank our patients for participating in this study.

AUTHOR CONTRIBUTION

Study concept and design: A.S.; drafting of the manuscript: G.S.; critical revision of the manuscript for important intellectual content: M.K.

CONFLICT OF INTEREST

There are no conflicts of interest between the authors.

ETHICAL STANDARDS

This study was approved by Islamic Azad University-Yazd Branch. All the patients signed written consent before including the study.

REFERENCES

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Williams obstetrics. 23rd ed. New York: McGraw-Hill;2010:544-62.
2. Matthey PW, Finegan BA, Finucane BT: The public's fears about and perceptions of regional anesthesia. *Reg Anesth Pain Med.* 2004;29(2):96-101.
3. Birnbach DJ, Browne IM. Anesthesia for obstetrics. In: Miller RD. Miller's anesthesia. 7th ed. Philadelphia: Churchill Living stone. 2010:2207-11.
4. Dahlke JD, Mendez-Figueroa H, Rouse DJ, Berghella V, Baxter JK, Chauhan SP. Evidence-based surgery for cesarean delivery: an updated systematic review. *Am J Obstet Gynecol.* 2013;209(4): 294-306.
5. American College of Obstetricians and Gynecologists: Fetal monitoring prior to scheduled cesarean delivery. 2010;382.

6. Dailey PA, Fisher DM, Schnider SM, et al. Pharmacokinetics, placental transfer and neonatal effects of vecuronium and pancuronium administered during cesarean section. *Anesthesiology*. 1984;60(6):569-74.
7. Basuni AS. Addition of low-dose ketamine to midazolam and low-dose bupivacaine improves hemodynamics and postoperative analgesia during spinal anesthesia for cesarean section. *J Anaesthesiol Clin Pharmacol*. 2016;32(1):44.
8. Wahi A, Singh AK, Syal K, Sood A, Pathania J. Comparative Efficacy of Intrathecal Bupivacaine Alone and Combination of Bupivacaine with Clonidine in Spinal Anesthesia. *JCDR*. 2016;10(4):06.
9. Freedman JM, Li DK, Drasner K, Jaskela MC, Larsen B, Wi S. Transient Neurologic Symptoms after Spinal Anesthesia: An Epidemiologic Study of 1,863 Patients. *J Am Soc Anesthesiol*. 1998;89(3):633-41.
10. Choi DH, Ahn HJ, Kim MH. Bupivacaine – sparing effect of fentanyl in spinal anesthesia for cesarean delivery. *Reg Anesth Pain Med*. 2000;25(3):40-5.
11. Apgar V. A proposal for a new method of evaluation of the newborn. *Classic Papers in Critical Care*. 1952;32(449):97.
12. Santhosh MC, Bidikar M, Mudakangoudar MS. Comparison of intrathecal levobupivacaine and levobupivacaine plus fentanyl for cesarean section.
13. Yousef AA, Salem H.A, Moustafa M.Z. Effect of mini-dose epidural dexmedetomidine in elective cesarean section using combined spinal-epidural anesthesia: a randomized double-blinded controlled study. *J Anesth*. 2015;29(5):708-14.
14. Zirak N, Hafizi L, Eftekharzadeh S, Ghomian N, Moradifar M. Evaluating the effect of regular dose plus fentanyl in spinal anesthesia of elective cesarean section on neonatal apgar score and time of sensory-block regression. *IJOGI*. 2012;15(20):12-8.
15. Rasooli S, Moslemi F. Comparison of prophylactic infusion of phenylephrine with ephedrine for prevention of hypotension in elective cesarean section under spinal anesthesia: a randomized clinical trial. *IJMS*. 2015;40(1):19.
16. Nair G, Abrishami A, Lermite J, Chung F. Systematic review of spinal anesthesia using bupivacaine for ambulatory knee arthroscopy. *Br J Anaesth*. 2009;102:307-15.
17. Sanli S, Yegin A, Kayacan N, Yilmaz M, Coskunfirat N, Karsli B. Effectiveness of hyperbaric spinal ropivacaine for cesarean section: with or without fentanyl. *Eur J Anaesthesiol*. 2005;22(6):457-61.
18. Jain K, Grover V, Mahajan R, Batra YK. Effect of varying doses of fentanyl with low doses spinal bupivacaine for cesarean delivery in patient with pregnancy-induced hypertension. *J Obstet Anesth*. 2004;13(4):215-20.