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Cardiovascular Effect and Duration of Analgesia in Spinal Anesthesia using Plain Bupivacaine and Plain Levobupivacaine with or without fentanyl

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ABSTRACT
Background: *Spinal anaesthesia is widely used in surgery of lower extrernity, caesarean section, surgery of the lower abdomen or surgery below the diaphragm where spinal anaesthesia is indicated.*
Objective: *To assess and compare the cardiovascular effects and duration of analgesia using bupivacaine and levobupivacaine in spinal anesthesia with or without fentanyl.*
Methods: *Patients were randomly assigned to four groups by card sampling method. Group- B (n=20) received plain bupivacaine 0.5% 2.5 ml, Group- BF (n=20) received plain bupivacaine 0.5% 2.2 ml + fentanyl 15 µgm, Group- L (n=20) received plain levobupivacaine 2.5 ml, Group- LF (n=20) received plain levobupivacaine 2.2 ml + fentanyl 15 µgm.*
Results: *The comparison of intraoperative heart rate and blood pressure status among the patients of different groups where it was observed Group-L and Group-LF showed more stable heart rate over time than Group-B and Group-BF. Heart rate remains unstable during the surgery in Group-B and Group-BF. The difference was significant (P<0.05). On the other hand, Levobupivacaine and Levobupivacaine with fentanyl showed more ionotropic effect than bupivacaine and bupivacaine with fentanyl. Blood pressure was found consistently higher in Group-L and Group-LF. And the difference was also found significant (P<0.05). Duration of block was found greater in Group-L and Group-LF where the difference was significant.*
Conclusion: *To the best of our knowledge, this is important research on comparison among different pattern of spinal drugs. It was observed that in terms of cardiovascular effect and duration of block, Levobupivacaine plus Fentanyl proclaimed the best performances, the differences were also statistically significant. Henceforth, it can be claimed here that further broad-spectrum study may be performed with large sample size and multi-disciplinary approach.*
Keywords: *Spinal anaesthesia, Bupivacaine, Levobupivacaine, Fentanyl.*

I. INTRODUCTION

The quest for researching newer and safer anaesthetic agent has always been one of the primary needs in anaesthesiology practice. Regional anaesthesia technique has seen numerous modifications over the last twO decades with the advent of many new and safer anaesthetics. Bupivacaine is considered the gold standard long-acting spinal anaesthetics. Levobupivacaine as a pure S-enantiomer of recemic bupivacaine is an attractive alternative to bupivacaine because its toxicity for CVS and CNS is lower. [1-2]Spinal anaesthesia is widely used in surgery of lower extremity, caesarean section, surgery of the lower abdomen or surgery below the diaphragm where indicated. Bupivacaine is the most popular anaesthetic for spinal anaesthesia. It is a long-acting amide local anaesthetic with duration of action of 2-3 hours. Bupivacaine is available in a preparation as a racemic mixture (50:50) of its two enantiomers levobupivacaine, S (-) isomer and dextrobupivacaine, R (+) isomer. Severe CNS and cardiovascular adverse reactions are reported that have been linked to the R (+) isomer of bupivacaine. The levobupivacain isomers were shown to have safer pharmacological profile and less cardiac adverse effects. [3]Levobupivacaine is relatively recently introduced local anaesthetic that is structurally similar to bupivacaine. Clinical studies all indicate that levobupivacaine is well tolerated and has efficacy equivalent to bupivacaine for anaesthesia and analgesia. [4] Levobupivacaine has been associated with less CNS and cardiac toxicity relative to bupivacaine when equal concentrations were compared. [5-6] But inadequate researches have been done comparing these two, i.e., bupivacaine and levobupivacaine when used along with fentanyl.Because of their close chemical relationship, levobupivacaine and racemic bupivacaine share many pharmacokinetic

properties but only one clinical study is available on intrathecal anaesthesia with levobupivacaine [7] suggesting that levobupivacaine achieves satisfactory anesthesia with an unpredictable spread of sensory blocked and the result were not compared with racemic bupivacaine. [8]

It has been documented that the combination of opiates and anaesthetic agents administered intrathecally has a synergistic effect that causes better and prolonged analgesia. [9] Moreover, use of opioids, i.e., fentanyl reduces the dose of bupivacaine as well as levobupivacaine. It also reduces the cardiovascular side effects significantly and provides better anaesthesia with faster onset. But very few comparative studies are present that included both bupivacaine and levobupicaine used with or without fentanyl.Fentanyl, administered intrathecally improves the quality of sensory blockade intraoperatively without increasing sympathetic or motor blockade, It also enhances the quality and duration of post operative analgesia to a significant extent. Fentanyl has no significant adverse outcome on the neonate. [10]There are cardiovascular side effects of spinal anaesthesia such as hypotension, bradycardia and less frequently cardiac arrhythmia and heart block. Hypotension is the most common cardiovascular complication of spinal anaesthesia.Addition of low doses of opioid to local anaesthetics used in spinal anaesthesia reduces the dose of local anaesthetics used. The incidence of adverse effect is also reduced, Titti et al. [11] reported that the rate of occurrence of hypotension was 62% in elective caesarean section in which they administered spinal anaesthesia with 2.5ml of 0.5% bupivacaine. In another study, [12] the incidence of hypotension with bupivacaine and fentanyl was found to be 36.69%. This difference might be due to decrease the dose of local anaesthetic and addition of fentanyl. The incidence of hypotension was significantly reduced to 16.6% in the doses when used in levobupivacaine group.This lack of comparative study leads us to investigate the cardiovascular effects and duration of analgesia of both bupivacaine and levobupivacaine when used with or without fentanyl by a prospective, double blind randomized trial. This in-depth study will help us to find out the appropriate drug or combination of drugs that has better analgesic profile and less prominent cardiovascular effects of spinal anaesthesia.

II. METHODOLOGY

This prospective randomized double blind trial study was carried out in the Department ofAnaesthesiology, Bangladesh Medical College Hospital, Dhaka, duringJuly 2016 to December 2016. A total of 80 patients were participated in the study. 80 Patients admitted for elective operations at in patient department (|PD) of urology surgery irrespective of sex in Bangladesh Medical College Hospital, Dhaka. Among them 20 patients were in Group-B, 20 patients were in Group-BF, 20 patients were in Group-L and 20 patients were in Group-LF. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24), where required.

III. RESULTS

4 groups	Drug	Dose
Group-B (n=20)	Plain bupivacaine (0.5%)	2.5ml
Group-BF (n=20)	Plain bupivacaine 0.5% + Fentanyl	2.2ml + 15mgm
Group-L (n=20)	Plain Levobupivacaine	2.5ml
Group-LF (n=20)	Plain Levobupivacaine + Fentanyl	2.2ml + 15mgm

Table 1: Demographic Data (n=80)

	Group-B (n=20)	Group-BF (n=20)	Group-L (n=20)	Group-LF (n=20)
Age (years)	26.19±2.93	24.97±3.15	29.11±5.75	32.77±4.98
Height (cm)	159.27±4.33	160.37±3.13	158.78±2.19	159.77±3.93
Weight (kg)	63.78±11.75	59.69±10.16	64.89±9.89	63.55±7.95
Duration of surgery (min)	88.55±10.73	92.73±9.15	87.69±11.77	90.64±7.53

Table-1 shows that among the demographic data of 80 patients all variables like age, height, weight and duration of surgery were comparable to another among Group B, BF, L and LF.

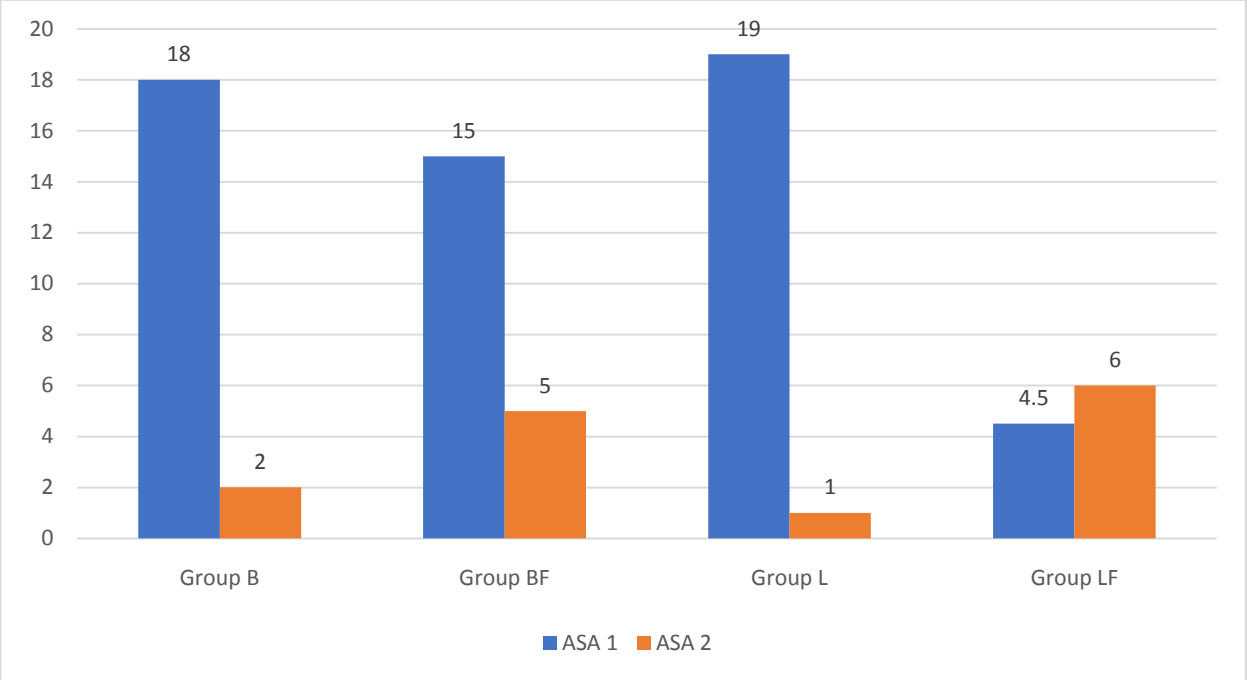

Fig 1: Distribution of patients according to ASA grading (n=80)

Fiqure-1 shows that out of 80 patients with 20 patients in each group, 90%, 75%, 95% and 70% patients were graded as ASA grade I in group B, BF, L and LF respectively on the contrary, 10%, 25%, 5% and 30% patients were graded as ASA Il in group B, BF, L and LF respectively.

Table 2: Intraoperative Heart Rate (n=80)

Minute	Group-B (n=20)	Group-BF (n=20)	Group-L (n=20)	Group-LF (n=20)	P value
3min	90±6.3	90±6.3	97±5.9	96±5.1	0.001^{s}
6min	94±5.4	92±5.9	96±3.3	96±5.7	0.001^{s}
9min	88±5.1	88±3.3	95±5.6	95±3.4	0.001^{s}
12min	87±6.3	85±5.5	93±6.2	94±5.3	0.001^{s}
15min	88±3.6	86±3.6	92±4.9	93±3.8	0.001^{s}
20min	85±4.1	89±6.5	90±4.3	92±3.3	0.001^{s}
25min	89±5.3	89±3.3	89±5.4	89±6.8	0.001^{s}
30min	94±4.9	94±3.4	87±5.4	89±5.7	0.001^{s}
35min	95±5.3	95±5.8	86±5.8	88±3.6	0.001^{s}
40min	96±5.9	95±4.8	85±3.7	85±6.8	0.001^{s}
45min	98±6.7	97±3.8	85±6.6	84±3.6	0.001^{s}
50min	95±6.1	92±6.4	86±5.6	84±6.4	0.001^{s}
55min	93±6.2	91±5.6	84±5.8	83±5.0	0.001^{s}
60min	90±5.4	88±4.7	84±4.7	82±5.5	0.001^{s}

Table-2 shows the actual comparison of introperative heart rate status among the patients of different groups where it was observed that the stability in groupL and LF were for better than group B and BF. These differences were found statistically significant (P<0.05).

Table 3: Intraoperative MAP (n=80)

Minute	Group-B (n=20)	Group-BF (n=20)	Group-L (n=20)	Group-LF (n=20)	P value
3min	85±7.9	82±6.9	100±7.1	99±4.8	0.001^{s}
6min	85±7.0	80±4.3	95±5.8	90±5.4	0.001^{s}
9min	78±5.9	80±6.7	90±5.2	89±5.6	0.001^{s}
12min	78±6.2	77±5.0	88±7.8	90±4.6	0.001^{s}
15min	76±6.5	76±7.1	85±8.0	86±7.1	0.001^{s}

20min	68±5.5	68±5.0	84±5.6	83±6.1	0.001[s]
25min	68±4.8	68±5.7	85±4.8	82±6.5	0.001[s]
30min	68±6.8	68±4.3	84±6.8	81±7.4	0.001[s]
35min	79±5.1	67±6.9	83±7.0	80±7.9	0.001[s]
40min	78±8.0	77±4.5	84±7.1	79±7.2	0.001[s]
45min	76±4.2	76±7.4	82±5.4	80±5.8	0.001[s]
50min	75±6.9	75±7.6	81±5.8	80±4.4	0.001[s]
55min	70±6.4	70±4.6	80±5.7	80±7.7	0.001[s]
60min	70±5.1	70±4.8	83±6.4	82±4.8	0.001[s]

Table 3 shows the actual comparison of intropeative blood pressure status among the patients of different groups where it was observed that the conditions in group L and LF were a little better than group B and BF. These differences were also statistically significant (P<0.05).

Table 4: Distribution of characterizations of sensory block (N=80)

Characteristics	Group-B (n=20)	Group-BF (n=20)	Group-L (n=20)	Group-LF (n=20)	P value
Time of onset of sensory block (min)	4.7±1.0	4.5±1.6	3.9±1.0	3.5±1.6	
Time For sensory block reach maximum (min)	7.7±1.6	7.6±0.9	6.9±06	6.8±1.1	
VAS Score after 1 hour	0.57±0.31	2.5±1.61	2.6±1.61	2.62±1.61	0.002[s]
VAS Score after 2 hours	0.6±0.4714	0.8±0.383	2±0.4714	1.2±0.4216	0.0001[s]
VAS Score after 3 hours	0.7±0.4630	0.4±0.5614	1.2±0.4089	2.1±0.4116	0.00027

Table 5: shows that the actual distribution of characterizations of sensory block.

IV. DISCUSSION

Levobupivacaine with fentanyl produces adequate levels of sensory blockade and also better haemodynamic stability when compared to bupivacaine with fentanyl. Gulen Guler et al. concluded that as side effects like hypotension, bradycardia and nausea are less, the combination of levobupivacaine + fentanyl (10mg /15 mcg) can be a good alternative. [13]

Previous studies reported that a spinal block higher than L1 would be adequate during TURP surgery, when bladder pressure is monitored and kept low. However, when intravesical pressure monitoring was not available - as in our study - a sensory block extending to T10 dermatome is necessary. [14] As known, systemic hypotension and bradycardia are the most common side effects during central neural blocks. Marked hypotension can be deleterious especially in geriatric patients with limited cardiac reserve. [15] High incidence of coronary disease in geriatric patients increases the risk of myocardial ischemia due to hypotension. Aside from age, a high level of block is another important factor in the development of hypotension during SA. In geriatric patients, gradual degeneration of peripheral and central nerves, changes in anatomical configuration of the lumbar and thoracic spine and the decrease in cerebrospinal fluid volume may contribute to this increase in sympathetic block level. [16]

Intrathecal opioids are known to enhance analgesia of subtherapeutic doses of local anesthetics. [17] Thus, successful SA can be achieved by combining intrathecal opioids with low doses of local anesthetics that would be inadequate when used independently.

In this study (Table-1), the mean age was almost similar among Group B, BF and L whereas in Group LF the mean age was the highest (32.77+4.98 years). The mean height and weight were almost same in all the groups. Duration of surgery revealed that the mean operation period was the highest in Group BF (92.73+9.15 min) which was subsequently followed by Group LF (90.64+7.53 min). Our study findings were agreed by a previous study though it was conducted to observe the effect of bupivacaine and levobupivacaine. [17]

This study included only American Society of Anesthesiologist (ASA) grade I and II. ASA grade III was excluded. However, the study of Zeynep N Akcaboy and his colleagues [18] included ASA grade III and IV in their study. Our results revealed that (Fgure-1) most of the cases of 4 groups were recognized as ASA grade l and among them Group L uphold the highest 19 (95%) patients. The previous study reported that ASA grade III was the highest in different groups of their study.

This study showed (Table-2) Group-L and Group-LF showed more stable heart rate over time than Group-B and Group-BF. Heart rate remains unstable over the time of surgery in Group-B and Group-BF. The difference was significant (P=<0.05)

This study reported that (Table-3) Levobupivacaine and Levobupivacaine with fentanyl showed more haemodynamic stability than bupivacaine and bupivacaine with fentanyl that was agreed by a previous study. [19] Blood pressure was found consistently higher in Group-L and Group-LF. But the difference was found also significant (P=<0.05).

A randomized, double-blind study of intrathecally administered 0.5% isobaric levobupivacaine or 0.5% hyperbaric bupivacaine in 70 patients scheduled to undergo elective transurethral endoscopic surgery found similar results between the two groups for the following variables: duration of sensory block, duration of two segment regression, time of onset and expiration of motor block, side effects, and pain scores at the beginning of the operation. [20] The authors suggested that 2.5 ml of 0.5% isobaric levobupivacaine and 0.5% hyperbaric bupivacaine provided the same clinical outcomes for spinal anaesthesia. [20]

In this present study, there were no significant differences between levobupivacaine and bupivacaine in terms of the sensory block scores following intrathecal injection. A prospective, randomized, double-blind study conducted in 50 patients who underwent urogenital surgery found no statistically significant differences in the sensory and motor block properties, as well as the haemodynamic effects, of 0.5% levobupivacaine and 0.5% bupivacaine; the authors suggested that levobupivacaine was an effective substitute for 0.5% bupivacaine. [21] Although animal research has demonstrated that the duration of sensory and motor block was similar for levobupivacaine and bupivacaine, there is some evidence of a small increase in duration of sensory block with levobupivacaine. In contrast, there is also evidence that levobupivacaine is less potent than bupivacaine.

The sensory blocking effects of bupivacaine and levobupivacaine were almost similar current findings (Table-4). In the levobupivacaine and Levobupivacaine +Fentanyl group, there was a relatively rapid onset of the sensory block level. It was also observed that duration of the block was also greater in the above-mentioned group and the difference was found significant. Some clinical studies suggest that the local anaesthetic effects of levobupivacaine are different from those of bupivacaine. Good hemodynamic stability with a reduced prevalence of side effects has been shown for intrathecal levobupivacaine in elderly patients. [22]

In this present study, the haemodynamic, sensory effects of intrathecal levobupivacaine and bupivacaine injections were compared with or without fentanyl and the combination of levobupivacaine and fentanyl knocked the best rank according to the results.

Limitations of the study

This is single centered study; duration is short and sample size is small. Sample taken from urology surgery only which might be extended to other discipline and does not proclaim the scenario of large population.

V. CONCLUSION

To the best of our knowledge, this is important research on comparison among different pattern of spinal drugs. It was observed that in terms of cardiovascular effect and duration of block, Levobupivacaine plus Fentanyl proclaimed the best performances, the differences were also statistically significant. Henceforth, it can be claimed here that further broad-spectrum study may be performed with large sample size and muti disciplinary approach.

VI. RECOMMENDATIONS

A multi-centered study in the divisional/ tertiary hospitals can reveal the real picture. The study period should be long. And multi-disciplinary (General surgery, gynae, orthopedics etc.) approach of research work can make the study precise and more authentic.

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