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Research Article

Epinephrine as Epidural Adjuvant to Bupivacaine and Fentanyl in Elective Orthopedic Surgeries

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Abstract: Epinephrine when used as an epidural adjuvant to thoracic epidural anesthesia was found to prolong the duration of anesthesia and also enhance the motor blockade. When it was used as adjuvant in labour analgesia it was found to have disadvantages of having denser motor block. The vasoconstriction and α2 agonism was the reason hypothesized to the above action of the epidural Epinephrine. Hence our study was designed to study the effects of Epinephrine in epidural anesthesia with Bupivacaine and Fentanyl in patients undergoing elective orthopedic surgeries in supine position. Study involved 40 patients, of whom 20 patients received 0.5% Bupivacaine with 1 µg/ml of Fentanyl and 5 µg/ml of Epinephrine and 20 of them, received 0.5% Bupivacaine with 1 µg/ml of Fentanyl. We compared the two groups for the onset of the sensory and motor block, degree of motor block, duration of analgesia and hemodynamics. From our study we could conclude that addition of Epinephrine at 5 µg/ml to 0.5% Bupivacaine and 1 µg/ml of Fentanyl resulted in enhancement of the onset of block, with higher degree of motor blockade. But the duration of analgesia was not enhanced by addition of Epinephrine.
Keywords: Epinephrine, Bupivacaine, Fentanyl, Epidural anesthesia

INTRODUCTION

Epinephrine has antinociceptive effect at the spinal cord level when used in conjunction with Bupivacaine and Fentanyl [1]. Connely et al concluded from their study that addition of Epinephrine at concentration of 5µg/ml together with 0.625 mg/ml Bupivacaine provided not only longer time to re-dose but also reduced the pain scores in patients receiving labour analgesia as compared to those receiving 0.625 mg/ml Bupivacaine alone [2]. R.M.Tackley *et al*. reported that alkalinized 0.5% Bupivacaine and Adrenaline was superior to 0.5% Bupivacaine alone for epidural anesthesia for Caesarean section as it produced a denser motor blockade [3]. Hence the study was designed to assess the effect of Epinephrine added in conjunction with Bupivacaine and Fentanyl in epidural anesthesia. Studies done on the epidural fentayl has shown a range of effective dosage from 1-10 micro g/ml. Curatolo *et al*. in their studies concluded epidural Adrenaline 100 microgram in saline did not have any serious adverse effects [4].

Aim of study

Prior institutional ethical committee approval was obtained for the study. The study was carried on as a prospective randomized double blinded study. Study was aimed to assess the quality of block obtained with Bupivacaine with Fentanyl as compared to Bupivacaine with Fentanyl and Epinephrine with respect to block onset and duration of sensory block, intensity and duration of motor block together with hemodynamics of the patients maintained during the block.

METHODOLOGY

Randomization was done based on www.randomization.com. 40 patients were randomized in two groups, Bupivacaine with Fentanyl group: containing 20 patients receiving 20 ml of 0.5% Bupivacaine with 1 micro g/ml of Fentanyl (BF group).

Bupivacaine with Fentanyl and Epinephrine group: containing 20 patients receiving20 ml of 0.5% Bupivacaine with 1 micro g/ml of Fentanyl and 5 micro g/ml of Epinephrine (BFE group).

Inclusion Criteria

- Adult patient 18 –60 years.
- Both sexes
- Patients belonging to American Society of Anesthesiologist physical status I& II
- Patients who gave their consent for the study.
- Patients undergoing elective orthopedic lower limb surgeries in supine position.

Exclusion Criteria

- Patient refusal for consent.
- Patients with known allergy to study drugs.
- Patients belonging to American Society of Anesthesiologist physical status III and IV
- Patient refusal for regional anesthesia
- Diabetics
- Hypertensive patients
- Local infection
- Those with contraindication for regional anesthesia
- Patients aged more than 60 years

All the patients were preoperatively assessed and appropriate investigations were done. Informed written consent was obtained from the patients.

Drugs Used

- Bupivacaine
- Fentanyl
- Epinephrine
- Atropine
- Ephedrine

Monitors Used

- Pulse Oximeter
- NIBP
- ECG

Methodology

Patients were randomized by computer generated randomization numbers and divided into Group BF and Group BFE. The study drug mixture was prepared with 19.5 ml of Bupivacaine with 0.4 ml of Fentanyl Citrate, and 0.1 ml of 0.9% Sodium Chloride or 0.1 ml of 1:1000 Epinephrine in a double blinded manner.

GROUP BF: 20 patients received 19.5 ml of Bupivacaine with 0.4 ml of Fentanyl Citrate, and 0.1 ml of 0.9% Sodium Chloride

GROUP BFE: 20 patients received 19.5 ml of Bupivacaine with 0.4 ml of Fentanyl Citrate, and 0.1 ml of 1: 1000 Epinephrine.

After ascertaining the inclusion criteria preoperative investigations were recorded preoperatively. Patients were connected to multi para monitor and ECG, Oxygen saturation (Pulse oximetry) and NIBP were monitored. Intravenous cannulation was carried out with 18G peripheral venous catheter. Baseline vitals such as pulse rate, blood pressure and oxygen saturation were recorded. Pre anesthetic check of Boyle's apparatus was done, Ambu bag, Airway gadgets, Emergency drugs were checked and kept available.

Under aseptic precautions, epidural catheterization was performed in the sitting position (after infiltration of 2ml of 2% Inj. Lignocaine) with 18G Tuohy needle by loss of resistance technique. 20G catheter was introduced in the epidural space.

The patients received 20 ml of study drug mixture, at the rate of 1 ml every three seconds after negative aspiration for blood and CSF. All the patients received supplemental oxygen and intravenous fluids.

Hemodynamics were monitored by means of pulse rate, systolic and diastolic blood pressures and oxygen saturation. Intraoperatively patients were monitored for onset and duration of sensory block, intensity and duration of motor block.

Definition of Variables

Sensory Block Onset Time: Time interval between end of anesthetic injection and appearance of cutaneous analgesia in dermatomes T-12, T-10, T-8.

Intensity of Motor Block: Intensity of motor block was assessed with Bromage motor scale.

Duration of Motor Block: Administration of anesthetic and attainment of grade I in Bromage motor scale

Post-OP Analgesia Duration: Administration of anesthetic and time of analgesic usage or top up dosing of epidural analgesia in PACU**.**

If there were hypotensive episodes, (measured as systolic blood pressure less than 30 % of its initial value or below 90 mmHg) during anesthesia, it was treated with administration of Ephedrine, 6 to 12 mg and increased administration of intravenous fluids.

Bradycardia (heart rate<45) were treated with Atropine, 0.6 mg, and administration of oxygen via face mask (4 l/min).

Statistical Analysis

It's a double blinded randomized controlled clinical study. Variables were analyzed with SPSS version 20 software. Quantitative variables were analyzed using independent "t" test, qualitative variables were analyzed using cross tabs. 'p' value less than 0.05 was taken as significant.

Patients were comparable in there baseline demographic parameters such as age, weight, height.

Mean age in BFE group was 39.1 years, and that in BF group was 42.25 years and the p value was statistically in significant. The mean height and weight in the BFE group were 66.05 kg and 165.9 cm as compared to BF group it was 69.95 kg and 169.35 cm which were also comparable and the variation was statistically insignificant.

Table 1: Demographic variables

Group	Mean age in years	Mean weight in kg	Mean height in cm
BFE	39.10	66.05	165.90
BF	42.25	69.95	169.35
p value	0.496	0.097	0.163

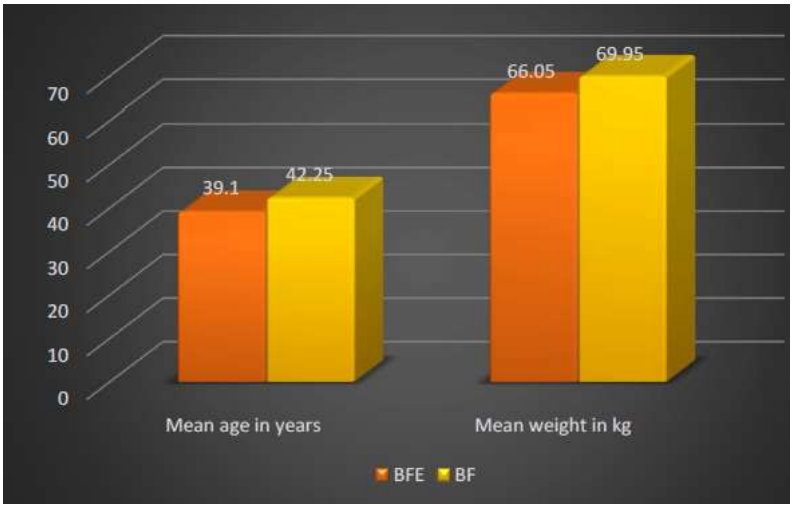

Fig. 1: Mean age and weight in the study groups

Fig. 2: Mean height of patients in both groups

Gender distribution in both groups were comparable with 16 male and 4 female patients in BFE group and 17 male and 3 female patients in BF group.

Table 2: Gender distribution

Group	Number of males	Number of females	Total
BFE	16	4	20
BF	17	3	20
p value	0.677		

Fig. 3: Gender distribution

15 patients in BFE group and 12 patients in the BF group belonged to American Society of Anesthesiologist physical status 1 group. 5 patients in BFE group and 8 patients in BF group belonged to ASA physical status 2 and the variance was of no statistical significance.

Table 3: ASA physical status among study groups

Group	Number patients of ASA 1	Number patients of ASA 2
BFE	15	5
BF	12	8
p value	0.311	

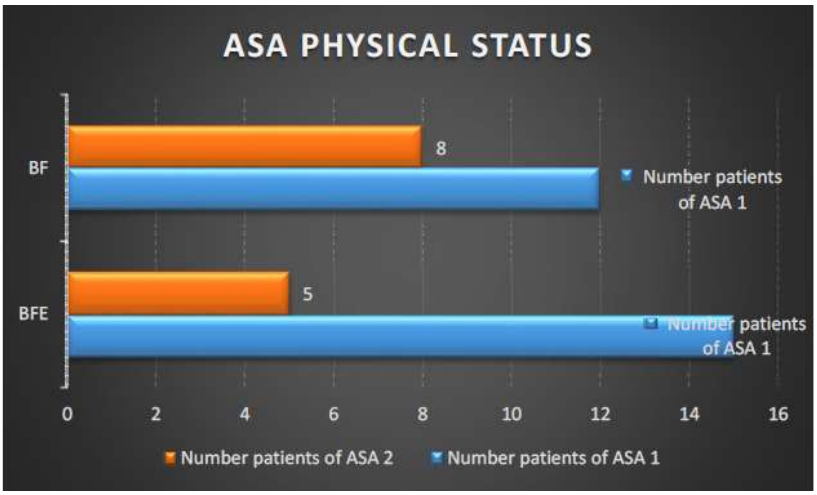

Figure 4: ASA physical status among study groups

Mean duration of surgery and length of epidural catheter in space were comparable in both groups, with mean duration of surgery being 177 minutes in BFE group and 171.75 minutes in BF group. The mean length of epidural catheter inserted in BFE group was 6.85 cm and that in BF group was 6.5 cm p value was found to be more than 0.05 and was statistically insignificant.

Table 4: Mean duration of surgery and length of epidural catheter in epidural space

Group	Mean duration of surgery in minutes	Mean length of epidural catheter in space
BFE	177	6.85
BF	171.75	6.50
p value	0.523	0.185

2 patients in both the study groups epidural catheterization was done at L1-L2 level, 10 patients in BFE group and 11 patients in BF group epidural catheterization was done at L2-L3 space, 8 patients in BFE group and 7 patients in BF group epidural catheterization was done at L3-L4 space. The variation in the site at which epidural catheterization done was not statistically significant with p value of 0.944.

Table 5: Space of epidural catheterization in study groups

Group	Level at which epidural catheter was inserted		
	L1-L2	L2-L3	L3-L4
BFE	2	10	8
BF	2	11	7
p value	0.944		

Mean time for onset of sensory block in the BFE group at T12, T10 and T8 dermatome were 10.85, 21.6, 36.25 minutes respectively. The mean time for onset of sensory block in BF group was 13.9, 27.35 and 42.3 minutes at T12, T10 and T8 dermatomes respectively. The variation in onset of block was statistically significant at all the three levels with p=0.000.

Table 6: Mean duration for onset of sensory block.

Group	Mean time of onset of sensory block in minutes		
	T12	T10	T8
BFE	10.85	21.6	36.25
BF	13.9	27.35	42.30
P value	0.000	0.000	0.000

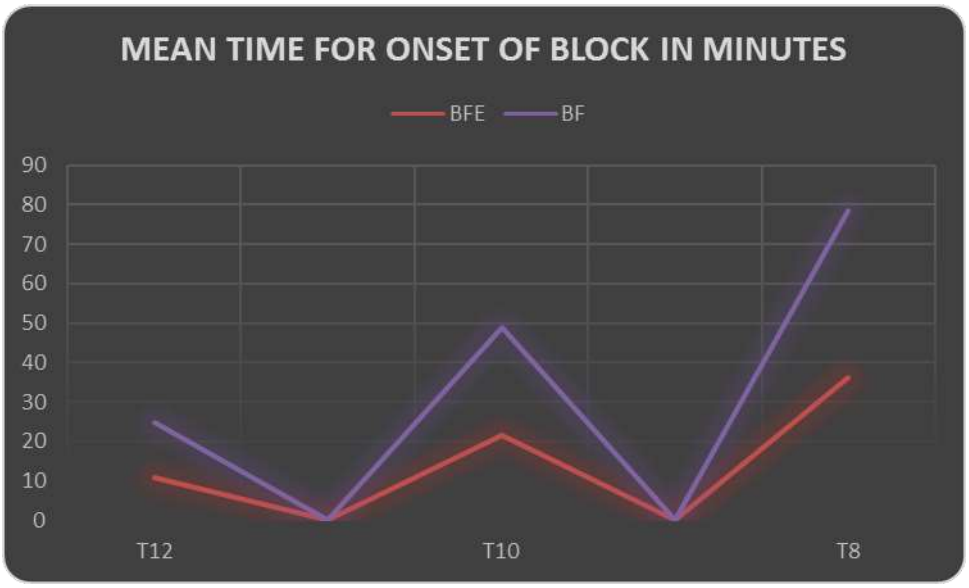

Figure 5: Mean duration for onset of sensory block

Mean time for regression of sensory block from T10-T12 in BFE group was 60.75 minutes and in BF group was 57.25 minutes and the p value for same is 0.310 which was not statistically significant.

Table 7: Mean duration for regression of sensory block from T12-T10 dermatome

Group	Time in minute for regression of sensory block from T10-T12
BFE	60.75
BF	57.25
p value	0.310

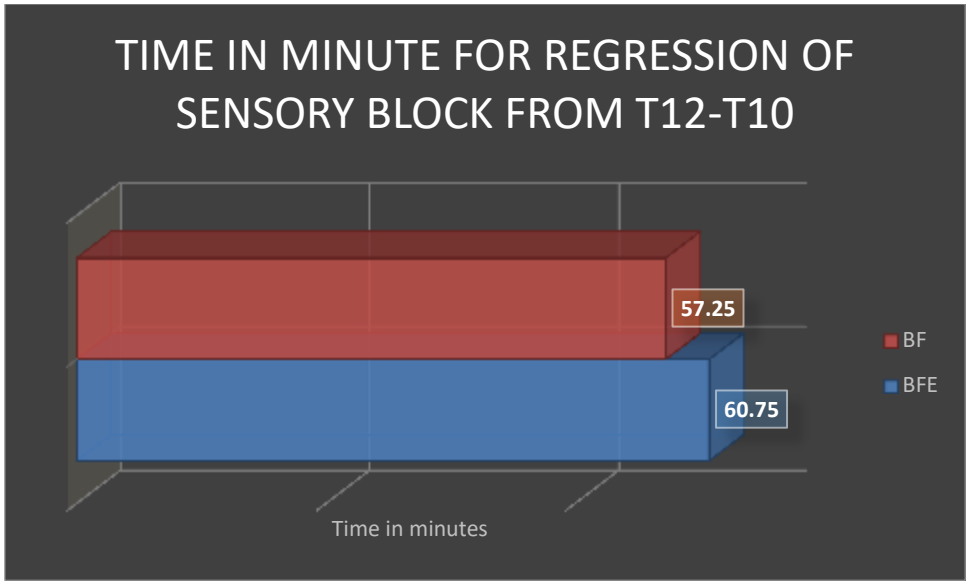

Fig. 6: Mean duration for regression of sensory block from T12-T10 dermatome

Mean duration of motor block in BFE group was 210 minutes and that in BF group was 204.65 minutes, the calculated p value was found to be 0.289 and was not statistically significant.

Table 7: Mean duration of motor block

Group	Mean duration of motor block in minutes
BFE	210
BF	204.65
P value	0.289

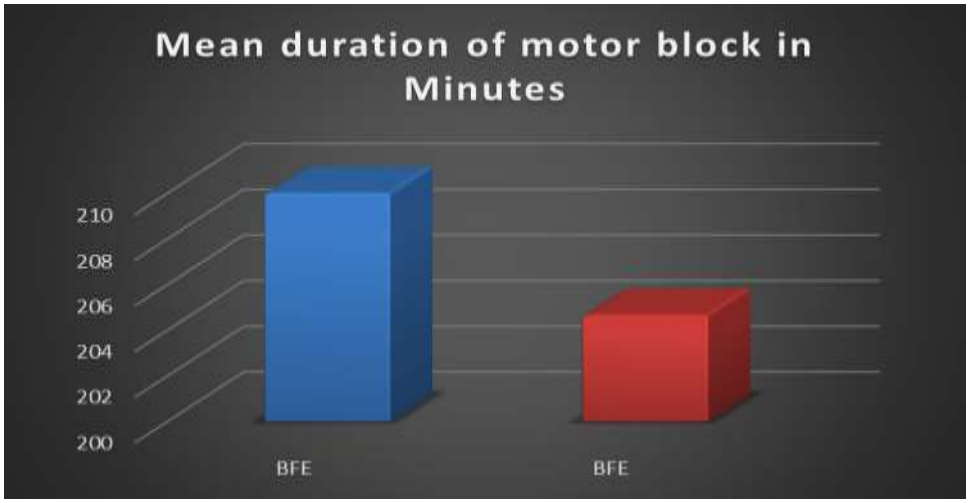

Fig. 6: Mean duration of motor block

Density of motor block was assessed with Bromage scale and it was found in BFE group 2 patients had motor block of grade 2, 16 patients had motor block grade3 and 2 patients had motor block grade 4. In BF group 8 patients had motor block of grade2 and 12 patients had motor block of grade 3, p value was found to be 0.046 and was statistically significant.

Table 8: Density of motor blockade as measured by Bromage scale

Group	Bromage score attained for motor blockade		
	2	3	4
BFE	2	16	2
BF	8	12	0
P value	0.046		

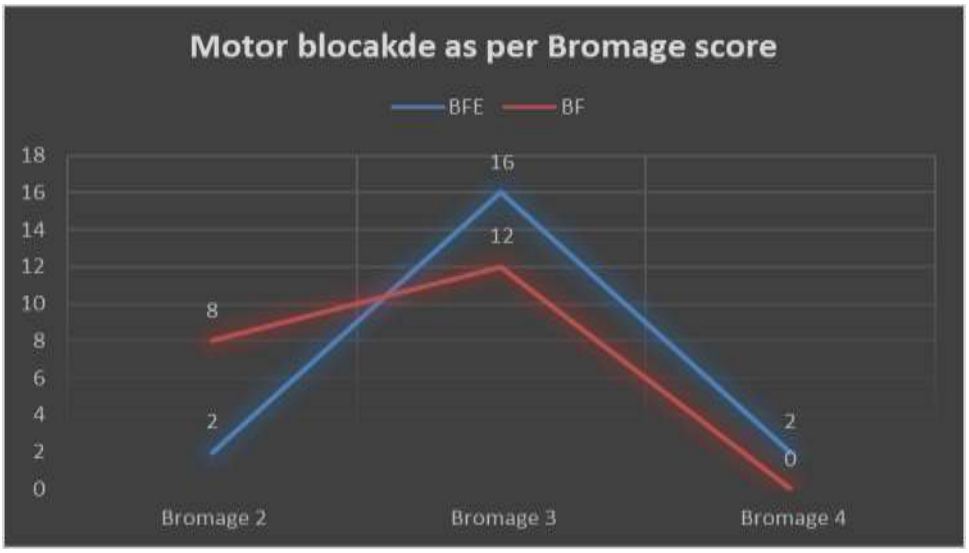

Fig. 7: Density of motor blockade as measured by bromage scale.

The pulse rate variation among the groups is as shown in table 9, and figure 8, the pulse rate variations between the group was found to be statistically insignificant with p value >0.05.

Table 9: Pulse rate variation among the study groups

Group	Pulse rate in beats per minute				
	At 1 min	**At 5 min**	**At 15 min**	**At 30 min**	**At 60 min**
BFE	82.9	88.7	86.75	86.35	86.25
BF	86.85	85.65	86.6	88.05	88.85
P value	0.346	0.412	0.970	0.704	0.417

Group	Pulse rate in beats per minute		
	At 120 min	**At 150 min**	**At 180 min**
BFE	83.35	82.85	83.4
BF	88.1	86.85	87.4
P value	0.183	0.260	0.250

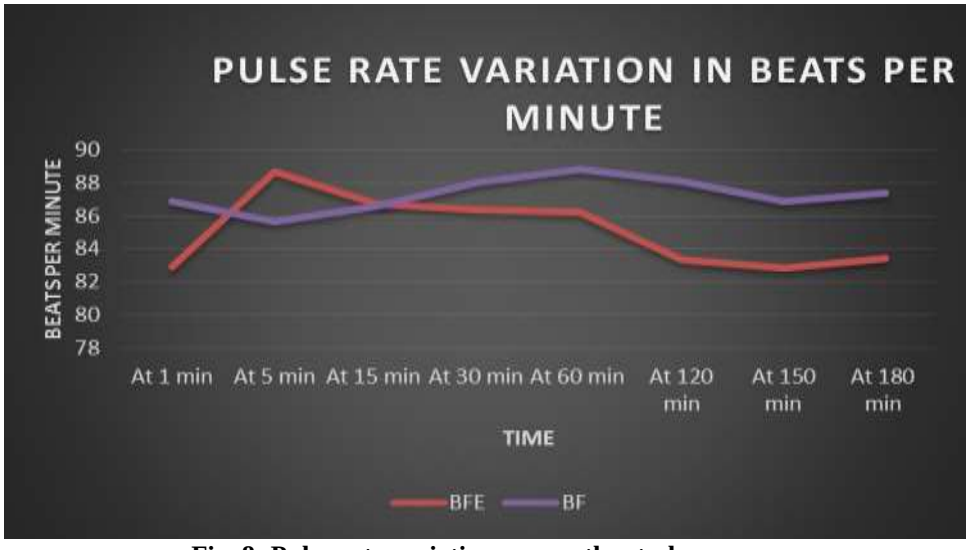

Fig. 8: Pulse rate variation among the study groups

The systolic blood pressure variation among the study groups are tabulated as in table 10, and figure 9, the systolic blood pressure in BFE group was found to be higher than that in BF group at 5 and 15 minutes which was statistically significant (p=0.043and 0.006) .

Table 10: Systolic blood pressure variation among the study groups

Group	Systolic BP in mm of Hg				
	At 1 min	At 5 min	At 15 min	At 30 min	At 60 min
BFE	137.60	130.4	132.25	125.40	122.25
BF	131.65	122.85	121.95	120.30	120.60
p value	0.110	0.043	0.006	0.269	0.695

Group	Systolic BP in mm of Hg		
	At 120 min	At 150 min	At 180 min
BFE	119.55	121.60	120.90
BF	117.80	120.50	119.30
P value	0.650	0.717	0.569

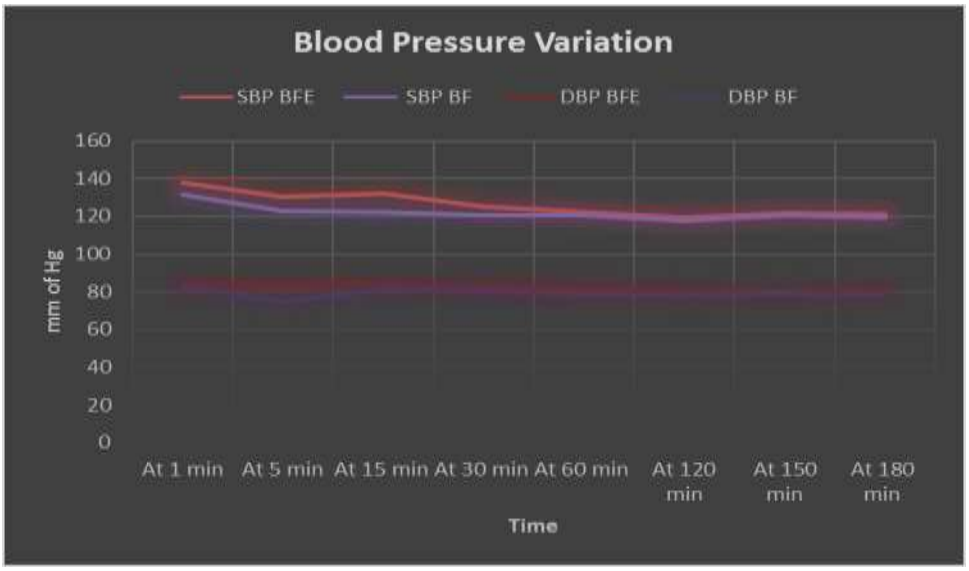

Fig. 9: Blood pressure variation among the study groups

The diastolic blood pressure variation among the study groups are tabulated as in table 11, and figure 9, the diastolic blood pressure in BFE group was found to be higher than that in BF group at 5 which was statistically significant with p=0.000

Table 11: Diastolic blood pressure variation among the study groups

Group	Diastolic BP in mm of Hg				
	At 1 min	At 5 min	At 15 min	At 30 min	At 60 min
BFE	83.35	82.70	83.80	82.40	81.30
BF	82.82	74.75	81.50	80.30	78.70
p value	0.805	0.000	0.325	0.417	0.347

Group	Diastolic BP in mm of Hg		
	At 120 min	At 150 min	At 180 min
BFE	79.45	78.60	80.60
BF	78.20	78.30	78.90
P value	0.599	0.888	0.469

3 patients in BF group had hypotension and were treated with Ephedrine, none of the patients in BFE group required Ephedrine (p=0.072). No patients in both group required Atropine for bradycardia.

Table 12: Requirement of Ephedrine

Group	Requirement of Ephedrine	
	Yes	No
BFE	0	20
BF	3	17
p value	0.072	

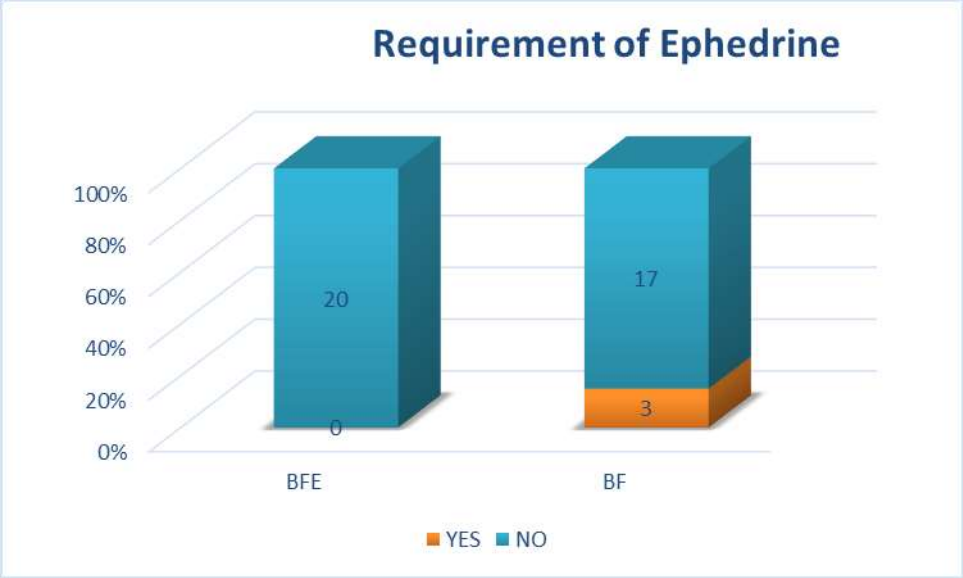

Fig. 10: Requirement of Ephedrine

Duration of analgesia in both the groups were comparable the variation was statistically insignificant.

Table 13: Duration of analgesia among the groups

Group	Duration of analgesia
BFE	309.05
BF	309.00
p value	0.994

RESULTS

We conducted double blinded randomized controlled study to find the efficacy of Epinephrine as epidural adjuvant to Bupivacaine in patients undergoing elective lower limb surgeries in supine position. 40 patients were randomly divided into two groups of 20 each. In BFE group patients received 0.5% Bupivacaine 1microgram/ml of Fentanyl together with 5 microgram/ml of Epinephrine, the BF group received 0.5% Bupivacaine 1microgram/ml of Fentanyl.

There was no significant difference between groups in distributions of age, weight, height and gender distribution, ASA physical status, type of surgery or duration of surgery. The groups were also comparable in terms of site of epidural catheterization and the length of epidural catheter fixed in space. Baseline pulse rate and blood pressure were comparable in both groups. Mean time for onset of sensory block in BFE group at T12, T10 and T8 were 10.85, 21.6 and 36.25 minutes respectively. The sensory block onset time BF group at T12, T10 and T8 were 13.9, 27.35 and 42.3 minutes, the onset time was statistically earlier in BFE group as compared to BF group at all the three levels with p value of 0.000. Mean systolic blood pressure in BFE group at 5^{th} minute and 15^{th} minute were 130.4 and 132.25 mm of Hg it was significantly higher as compared to BF group in which mean systolic blood pressure at 5^{th} and 15^{th} minute were 122.85 and 121.95 mm of Hg (p=0.043, 0.006). Mean diastolic blood pressure in BFE group (82.7mm of Hg) was higher than BF group at 5^{th} minute (74.75 mm of Hg) with the p value of 0.000 and was statistically significant. Motor block was assessed with bromage score and was found that the block intensity was denser in BFE group than BF group with p value of 0.046 and was statistically significant. Regression time of block from T10-T12 in BFE group was 60.75 minutes and that in BF group was 57.25 minutes variation between groups was not statistically significant with p value of 0.310. Duration of motor block in BFE group was 210 minutes and in BF group it was 204.65 minutes p value was found to be 0.289 and was statistically in significant. Duration of analgesia was similar in duration in both groups.

DISCUSSION

Addition of Epinephrine 5 microgram/ml to an optimally titrated thoracic epidural analgesic infusion of Bupivacaine 5 mg/ml and Fentanyl 1 micro g/ml hastened the onset of anesthesia and intensified the motor block. Vasoconstriction caused by Epinephrine is hypothesized to be the main cause of the observed beneficial effect of Adrenaline on the analgesia. The reduction of epidural blood flow by Adrenaline impedes systemic absorption of Fentanyl and local anesthetics and reduces their serum concentration [5-10]. By delaying the removal of Bupivacaine and Fentanyl from the epidural space, Adrenaline increases their concentration locally to reaches the spinal cord and spinal nerve roots, resulting in a more intense and prolonged analgesic effect covering more spinal segments. When an epidural infusion of Adrenaline with a local anesthetic and a lipophilic opioid is discontinued the increased epidural perfusion increases systemic absorption [11].

In a recent multicentric study with local anesthetic and lipophilic opioid it was found that the addition of Epinephrine decreased the dosage of the local anesthetic and increased the rapidity of discharge from hospital with no significant side effects [11].

Nearly from one century it is proven that Adrenaline given into the cerebrospinal fluid causes a profound antinociceptive effect [12]. Adrenaline alone (200–1000 microgram) injected into the lumbar cerebrospinal fluid caused spinal analgesia sufficient for vaginal delivery, without any clinical signs of spinal cord ischemia even after 1000 microgram [13]. Adrenaline produces analgesia through an alpha2-adrenergic mechanism in the substantia gelatinosarolandi of the spinal cord dorsal horn [14, 15]. When 50–100 microgram of Epinephrine is given alone epidurally, it has a weak hypalgesic effect [4, 16]. Adrenaline is metabolized by catechol-O-methyl transferase in spinal meningeal cells [17]. Therefore, the small dose of Adrenaline in our triple epidural analgesic mixture may not reach the spinal cord in a sufficient amount to activate spinal cord alpha2 receptors. However, even a weak subclinical analgesic effect may cause a significant synergistic effect when combined with drugs causing analgesia by different mechanisms of action [18]. Because Epinephrine, Fentanyl, and Bupivacaine have separate pharmacodynamic mechanisms of effect of nociception at the spinal cord level, supra-additive analgesic interactions are proposed to occur. This has been documented in neurophysiological animal studies with direct spinal cord application of such drugs [19]. Bromage *et al*. and Curatolo *et al*. concluded from their study that Adrenaline 50–100 microgram alone in an epidural bolus had only weak but detectable analgesic effects, and epidural infusion of Adrenaline alone at 20 microgram/hour clearly must be insufficient for pain relief after major surgery [4, 16]. Therefore, in addition to the vasoconstrictive pharmacokinetic interaction discussed previously, a supra-additive spinal cord pharmacodynamics analgesic interaction may be present among Epinephrine, Fentanyl, and Bupivacaine in this epidural analgesic mixture. Potent constrictive action of Epinephrine on vessels outside the central nervous system has led to concern that the blood supply of the spinal cord could suffer. However, there are no human data supporting this concern.

Table 14: Description of the Bromage score used in the study

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0%)
II	Just able to flex knees with free movement of feet	Partial (33%)
III	Unable to flex knees, but with free movement of feet	Almost complete (66%)
IV	Unable to move legs or feet	Complete (100%)

CONCLUSION

Addition of Epinephrine in concentration of 5 microgram/ml to 0.5% Bupivacaine and 1 microgram/ml of Fentanyl cause early onset of epidural anesthesia, denser motor block with no significant prolongation in duration of analgesia.

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