Original Research Article

Comparative study of the effects of intrathecal clonidine and fentanyl as adjuvant with low dose hyperbaric bupivacaine for unilateral spinal anaesthesia in lower limb surgery

Sarmila Guha Banerjee[1], Pratibha Bhunia[2*], Sonali Chatterjee[3], Sudakshina Mukherjee[4]

[1]Associate Professor, Department of Anaesthesiology, Medical College and Hospital, Kolkata, West Bengal, India
[2]Assistant Professor, Department of Anaesthesiology, Medical College and Hospital, Kolkata, West Bengal, India
[3]Senior Resident, Department of Anaesthesiology, Medical College and Hospital, Kolkata, West Bengal, India
[4]Professor and Head, Department of Anaesthesiology, Santiniketan Medical College, West Bengal, India

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Abstract

Background and Aims: Unilateral Spinal anaesthesia with bupivacaine is administered for lower limb surgeries. The aim of the study is to compare between the effects of Clonidine and Fentanyl when added as an adjuvant to low dose bupivacaine in unilateral spinal anaesthesia in lower limb surgery on the basis of onset and duration of sensory and motor blockade and post-operative analgesia. **Material & Methods**: After obtaining the institutional ethics committee approval total 150 patients ofeither sexbetween 18 to 55 years of age, American Society of Anaesthesiology (ASA) I and II scheduled for elective lower limb surgery were divided into three groups. All patients received 0.5% hyperbaric bupivacaine (7.5mg) 1.5ml intrathecally along with ± adjuvant (In Group A - clonidine (30 microgram) 0.2 ml diluted with normal saline to make 0.5 ml, Group B- fentanyl 25 microgram or 0.5 ml, Group C only 0.5ml normal saline) to make total 2ml solution . The results of observations were tabulated, compiled and statistically analysed using SPSS (version) 25.0 and Graph Pad prism version 5. **Result** : Fentanyl and clonidine both when added to low dose bupivacaine in unilateral spinal anaesthesia prolonged the duration of sensory and motor block compared to only low dose local anaesthetic agent. The time duration before the use of first dose of rescue analgesic is more prolonged in the group receiving clonidine as compared to Fentanyl group patient.

Key words: Unilateral spinal anaesthesia, Fentanyl, Clonidine,Bupivacaine, Quality of block.

Introduction

Unilateral spinal anaesthesia is commonly used for unilateral lower limb surgeries because of its reliability,provision of excellent surgical anaesthesia and prolonged post-operative analgesia[1]. Bupivacaine, an amide group local anaesthetic, is the most common drug being used intrathecally. However, high doses may lead to myocardial depression, heart blocks, dysrhythmias and even cardiac arrest. Thus with lower dose of bupivacaine for production of excellent surgical anaesthesia and post-operative analgesia a number of adjuvants have been used[2]. Opioid adjuvants produce a synergistic effect acting directly on opioid receptor in spinal cord.Fentanyl,a short acting lipophilic opioid stimulates the alpha 1 and alpha2 receptor and potentiates afferent sensory blockade and facilitates reduction in the dose of local anaesthetic without intensifying the motor block[3]. Clonidine is an alpha 2 agonist prolongs the duration of block believed to be due to direct effect on spinal cord mediated via alpha 2 post-synaptic receptor within dorsal horn.

The study was undertaken to compare the effects of clonidine when used as adjuvant in unilateral spinal anaesthesia to fentanyl used for the same on the basis of onset and duration of motor and sensory block and post-operative analgesia.

Materials and methods

A prospective, double blind randomised controlled study was performed from May 2018 to April2019 in our tertiary centerafter obtaining the institutional ethics committee approval. Total of 150 consenting patients of either sex, aged between 18 to 55 years of American Society of Anaesthesiology (ASA) I and II scheduled for elective unilateral lower limb surgery of less than 2 hours duration were selected for the study. Unwilling patients, incapable of giving consent due to physical or mental illness, patients having allergy to any study drug, with local infection or bleeding disorder, with history of drug or alcohol abuse, raised intracranial pressure, with previous neurovascular deficit were excluded from the study.

The primary outcome or objective on which the sample size calculation has been done is the duration of the sensory spinal block. Presuming a 25% difference in time in the mean duration ofspinal sensory block between groups to be clinically significantwith a power of0.8at 0.05 level of significance andasamplesizeof50patients in each groupwererequired.A total of 150 patients were chosen and randomly allocated to three group via computer generated random number list and allocation concealment was done serially numbered opaque sealed envelope technique.

The patients were explained priory about the procedure and also the Visual Analogue Scale (VAS) for pain assessment and consent was taken before they underwent the procedure. The quality of analgesia thus was assessed by VAS[4,5,6] (0-- No pain.1-3—Mild pain.4-6—Moderate pain.7-10—Severe pain. The routine preanaesthetic check-up was conducted for selection of the patient under study in accordance with inclusion and exclusion criteria.

Patients in each group received tab Diazepam 5 mg at the night before surgery and tab Ranitidine(150 mg)-1 tab night before surgery and another Ranitidine tab in the morning of surgery. On entering the operation theatre the patients were explained the procedure once again and the several basic monitors pulse oximeter, blood pressure cuff, electrocardiogram leads are attached to the patient for monitoring vital parameter like oxygen saturation, blood pressure and electrical activity of heart.

An intravenous(IV) line was secured over the forearm and iv fluid ringer lactate was started. Next the patient was placed in lateral decubitus with the operative side in dependant position. The patient was asked to flex his/her hip or knees close to chest as much as

*Correspondence
Dr. Pratibha Bhunia
Assistant Professor, Department of Anaesthesiology, Medical College and Hospital, Kolkata, West Bengal, India
E-mail: pratibhabhunia1986@gmail.com

possible. Strict asepsis was maintained, dressing and draping was done. The best possible inter-space was palpated on the spine and marked L3-L4 interspace. Next with the help of a Quinckes'25 gaugespinal needle the space was approached via midline with the bore of needle facing to the operative side and the drug was delivered. The drug was prepared in accordance with the following distribution of groups.

Gr A: received unilateral spinal anaesthesia with heavy Bupivacaine (1.5 ml) or 7.5 mg with clonidine (30 microgram) 0.2 ml diluted with normal saline. Clonidine 0.2 ml (150 microgram/ml)of the drug was taken in 1ml syringe aseptically prepared and diluted with 0.3 ml normal saline drawn to amount of 0.5 ml.This 0.5 ml adjuvant was added to 1.5 ml (7.5mg) 0.5% heavy bupivacaine for intrathecal injection.Strict asepsis was maintained during drug preparation and injection.

Gr B: received unilateral spinal anaesthesia with 0.5% heavy bupivacaine(7.5mg) or 1.5 ml with adjuvant Fentanyl 25 microgram or 0.5 ml. Fentanyl(0.5ml) was added to 1.5 ml heavy bupivacaine.Gr C: received unilateral spinal anaesthesia with bupivacaine heavy 0.5%(7.5mg) or 1.5 ml diluted to 0.5 ml with normal salineand without any adjuvant.

The drugs were prepared by anaesthesiologists taking care that the patients as well as the observars were not informed of the selected group specific drug given. The lateral decubitus was maintained for next 10 minutes.At the end of the same time period the patients were positioned supine for surgery and assessed for adequacy of surgical anesthesia .Adequacy of block was assessed according to need for supplementary analgesic and anaesthetic requirements;adequate if none needed , inadequate if only analgesic(fentanyl)needed and failed if general anaesthetic drugs required to complete the surgery.

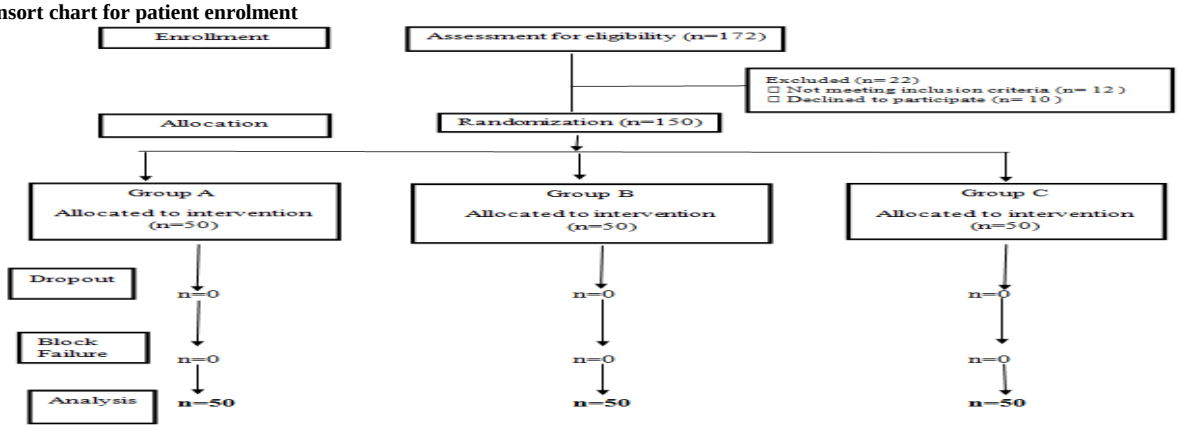
The sensory block was assessed by pin-prick method over the dermatomal region after the completion of intrathecal injection.A dull sensation to pin-prick to complete loss of sensation to pin prick was taken as positive.Assessment of the motor block was done after completion of intrathecal injection.The motor block was assessed by the Bromage ScoreGrade(criteriaI—Free movement of leg and feet.II—Just able to flex knee with free movement of feet.III—Unable to flex knees but with free movement of feet.IV—Unable to move legs or feet.)The duration of sensory block is defined as the time interval between the end of local anaesthetic administration and the complete resolution of anaesthesia on all nerves (regression of height of block) necessitating the use of analgesic.The duration of motor block is defined as the time interval between the end of local anaesthetic administration and complete recovery of motor function of the limb.Onset of motor and sensory block,duration of motor and sensory block and complications in 3 groups of the patients were studied.

The haemodynamic parameters were recorded at 5 min interval for 20 min and then every 15 min interval until the end of surgery and regression of block to L2 level.Hypotension was labelled as significant when fall in blood pressure was found to be greater than 30% from the preoperative MAP(mean arterial pressure).Hypotension was treated with incremental dose of vasopressor inj Mephentermine 6mg. Bradycardia was considered significant for recording of heart rate below 50 beats per minute and treated with inj Atropine 0.6 mg IV.The spinal anaesthesia was termed as unilateral when sensory block was found to be up to or above T12 level and Bromage score for motor block was greater than 2 on the operative side with no or detectable sensory or motor block of the other opposite limb. After operation patients were shifted to the wardand assessed for the duration of analgesia as per the VAS from 0 to 10 at the interval of 1 hour for 6 hours post operatively.The numeric activity was recorded post-operatively for all scores of 4 and above. The rescue analgesic was given in the form of inj Diclofenac I.M(intramuscular)along with1.5 mg/kg. Inj Ranitidine .All the patients were observed for side effects if any—hypotension, bradycardia,post-operativenausea,vomiting,shivering,dryness ofmouth,sedation.Shivering was managed with oxygen inhalation given via nasal prongs or cannulaand inj Tramadol 50 mg along with inj Ondasetron 8 mg IV.

Results and analysis

Duration of study was 12months.The results of the observation thus obtained in each group of the patient were tabulated, complied and statistically analysed using SPSS 24.0 and Graph pad prism version 5.The power of study was kept at 80% with type 1 error of 5%. The confidence limit of 95%,p value of <0.05 was considered significant. Our study followed the consort chart of randomisation.

Consort chart for patient enrolment



In our study we had taken 150 patients belonging to ASA I and ASA II in the age group of 18-55 years. Out of 150 patients 77 were male(51.4%) and 73 were female (48.6%). No difference in age weight, height, female to male ratio distribution and duration of surgery was obtained between the groups. In most of the patients surgery could be completed without analgesic supplementation. Only two patientsof group C required fentanyl till end of surgery. Following parameters were analysed like onset and duration of sensory block, onset and duration of motor block, duration of postoperative analgesia, hemodynamic parameters and any adverse events. Patient's characteristics were analysed with kruskal-wall is test. Hemodynamic changes were analysed by ANOVA. Chi-square test was used to analyse dichotomous variables. In group A, the mean sensory onset of patients was 8.6800 ± 1.5706(in minutes). In group B, the mean sensory onset (mean ± s.d.) of patients was 8.1200 ± 1.7100 (in minutes).In group C, the mean sensory onset of patients was 8.2000 ± 1.3093 (in minutes). Distribution of mean sensory onset vs groups were not statistically significant (*p* value =0.2354). (s.d=standard deviation)

Table 1: Distribution mean SEN ON (Mean sensory onset in minutes)

		Number	Mean	SD	Minimum	Maximum	Median	*p* value
MOT ON or motor onset	Group A	50	8.6800	1.5706	5.0000	12.0000	9.0000	0.2354
	Group B	50	8.1200	1.7100	5.0000	13.0000	7.0000	
	Group C	50	8.2000	1.3093	6.0000	11.0000	8.0000	

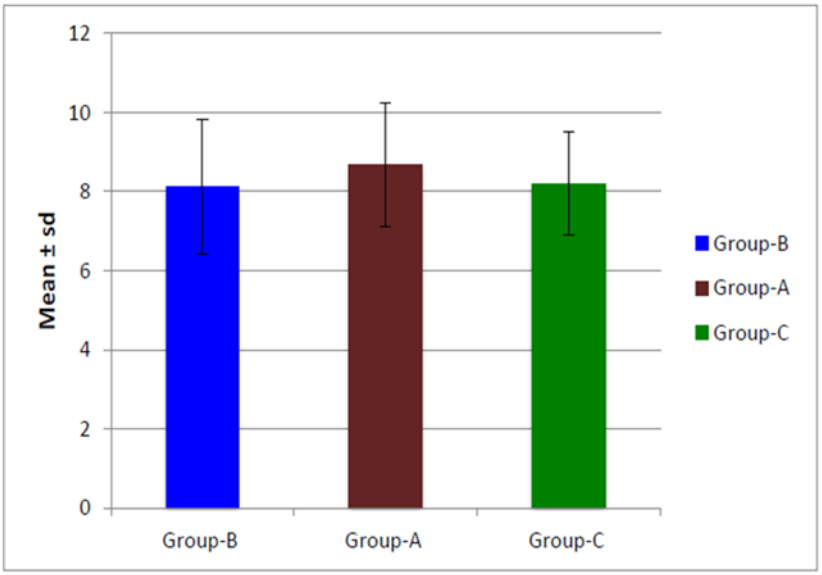


Figure 1: **Distribution of mean sensory onset (min) vs groups**

Onset of motor block denotes time taken for complete motor block after spinal injection on the operative sides.In group-B, the mean motor onset (mean±s.d.) of patients was 9.0000 ± 0.9476(in minutes).In group-A, the mean motor onset (mean±s.d.) of patients was 8.9400 ± 1.3614 (in minutes).In group-C, the mean motor onset (mean±s.d.) of patients was 9.3800 ± 2.1936 (in minutes).Distribution of mean motor onset vs. group was not statistically significant (p value=0.8450).

Table 2: Distribution mean MOT ON (Mean Motor onset in minutes)

		Number	Mean	SD	Minimum	Maximum	Median	*p* value
MOT ON or motor onset	Group A	50	8.9400	1.3614	5.0000	10.0000	7.0000	0.8450
	Group B	50	9.0000	0.9476	7.0000	11.0000	9.0000	
	Group C	50	9.3800	2.1936	7.0000	19.0000	9.0000	

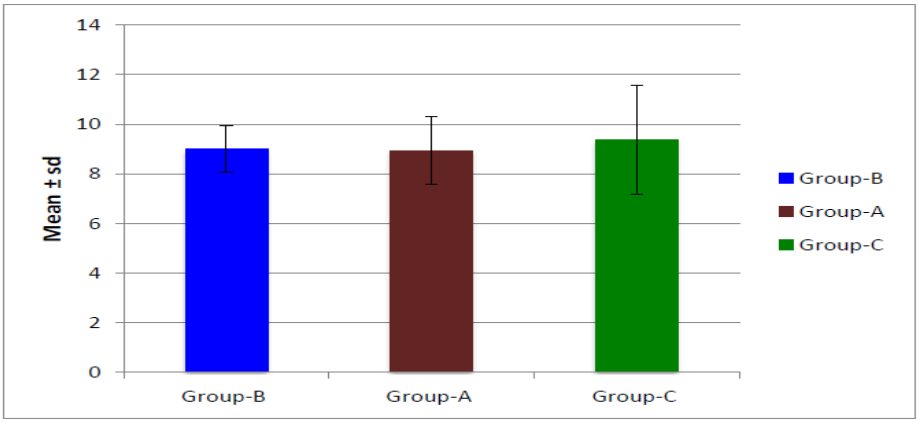


Figure 2: **Distribution of mean motor onset (min) vs groups**

Sensory duration represented time taken for two segments regression of sensory block from the highest level of block in the operative side. Mean sensory duration of three groups were Compared. It was seen that mean sensory duration of Group A was more (140.0800min)than the other groups(Group B-124.0600min,Group C-110.5000min) and that was statistically significant(*p value*<0.0001).

Table 3: **Distribution mean SEN DUR (Mean Sensory duration in minutes).**

		Number	Mean	SD	Minimum	Maximum	Median	*p* value
SEN DUR Or SENSORY DURATION	Group A	50	140.0800	7.4556	124.0000	153.0000	140.0000	<0.0001
	Group B	50	124.0600	7.6356	108.0000	144.0000	124.0000	
	Group C	50	110.5000	9.7127	88.0000	126.0000	110.0000	

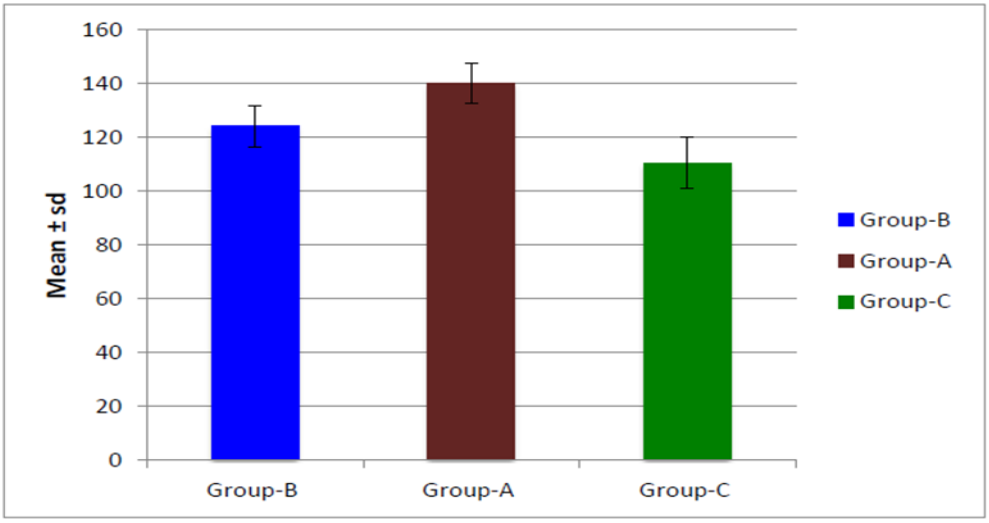


Figure 3: Distribution mean SEN DUR (Mean Sensory duration in minutes).

Mean motor duration denoted time taken for complete motor recovery after complete motor block in the operative side. In our study mean motor duration (min) of three groups were compared. In group A mean motor duration of patients was prolonged (263.8800min±21.9411) than group B(193.1400min±19.490)and group C(167.5400min±7.5626) that was statistically significant(*p value*<0.0001).

Table 4: **Distribution of mean MOT DUR (Mean Motor duration in minutes).**

		Number	Mean	SD	Minimum	Maximum	Median	*p* value
MOT DUR Or MOTOR DURATION	Group A	50	263.8800	21.9411	199.0000	299.0000	266.5000	<0.0001
	Group B	50	193.1400	19.4905	131.0000	244.0000	194.5000	
	Group C	50	167.5400	7.5626	143.0000	180.0000	169.0000	

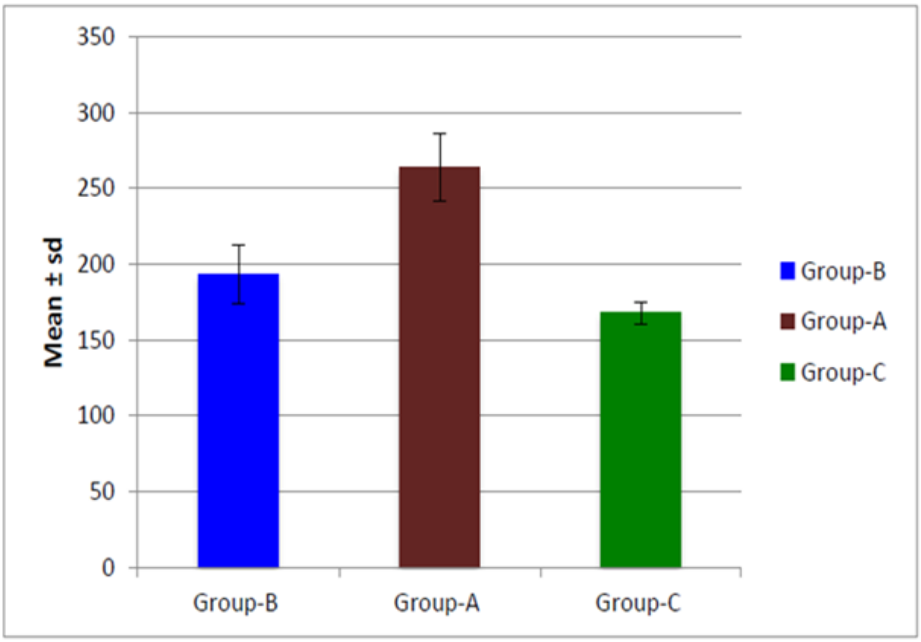


Figure 4: **Distribution of mean MOT DUR (Mean Motor duration in minutes).**

Next distribution of mean analgesia duration was compared in three groups. Mean analgesic duration defined duration from spinal injection till the first dose of rescue analgesic was given (minutes).In group A the mean analgesia duration of patients was 356.1400 ± 12.9379(in minutes). In group B, the mean analgesia duration (mean ± s.d.) of patients was 309.3600 ± 17.5252 (in minutes).In group C, the meananalgesia duration of patients was 226.9800 ± 11.3542 (in minutes). Distribution of meananalgesia duration of patients vs groups were statistically significant.(*p value*-<0.0001)

Table 5: **Distribution of mean ANA DUR (Mean Analgesia duration in minutes).**

		Number	Mean	SD	Minimum	Maximum	Median	*p* value
ANA DUR Or Analgesia Duration	Group A	50	356.1400	12.9379	319.0000	378.0000	358.5000	<0.0001
	Group B	50	309.3600	17.5252	261.0000	341.0000	311.0000	
	Group C	50	226.9800	11.3542	202.0000	243.0000	228.0000	

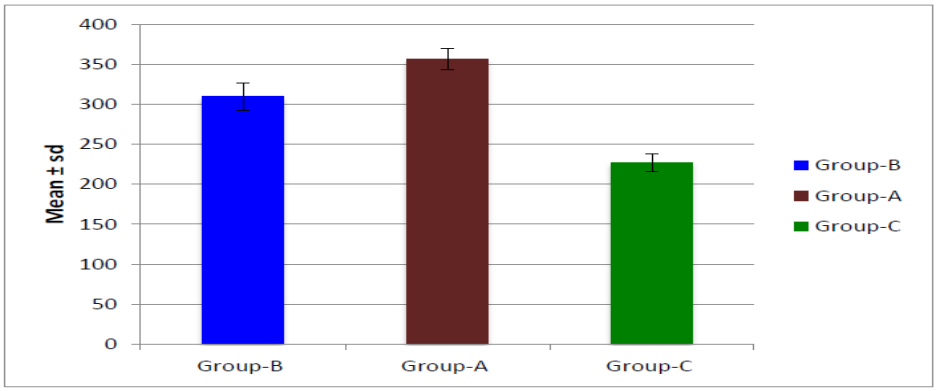


Figure 5: **Bar diagram showing mean analgesic duration in minutes for each group**

Intraoperative hemodynamic parameter were recorded and analysed. Changes in pulse rate, systolic and diastolic blood pressure during intraoperative period were compared in three groups.Association Of hemodynamic parameters vs. groups were not statistically significant.*(p value*>0.05).

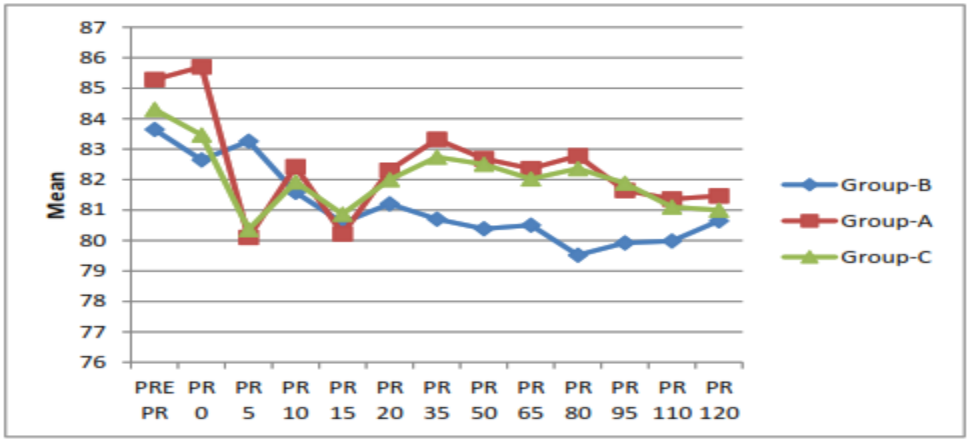


Figure 6: Line chart showing the distribution of mean pulse rate (mm of Hg) in different time intervals (in minutes)

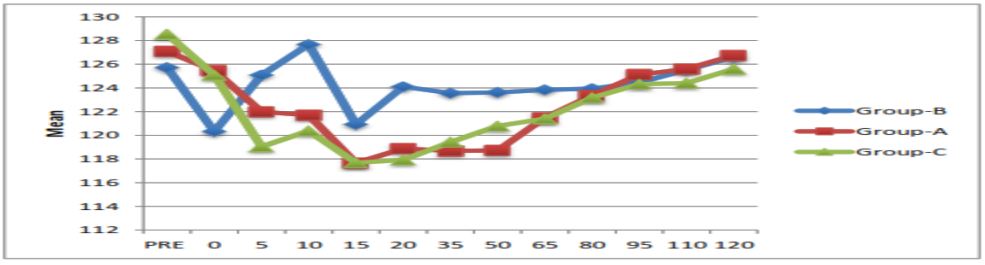


Figure7: Line chart showing the distribution of mean systolic blood pressure (mm of Hg) in different time intervals (in minutes)

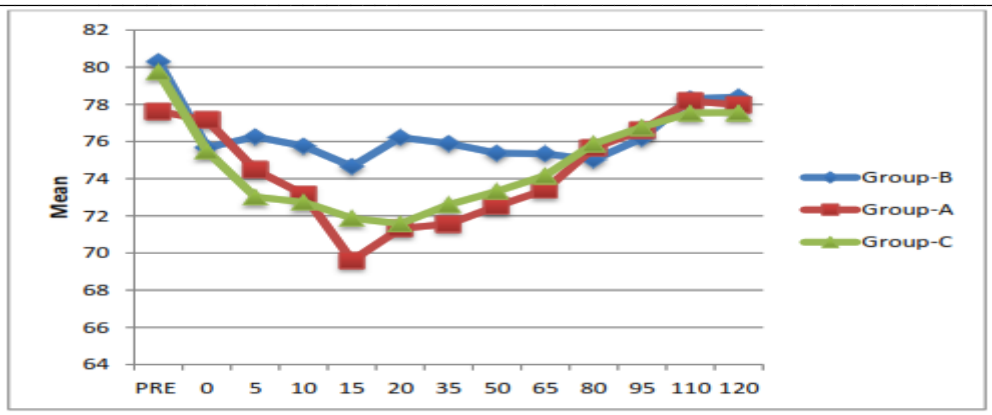


Figure 8: Line chart showing the distribution of mean diastolic blood pressure (mm of Hg) in different time intervals (in minutes)

Table 6: Occurrence of complications among the groups

Complications	Group A (n=50)	Group B	Group C	*p* value
Hypotension	3 (6%)	2 (4%)	2 (4%)	0.8608
Bradycardia	1 (2%)	1 (2%)	0	0.6024
Shivering	1 (2%)	0	1 (2%)	0.6024
Post-operative nausea and vomiting	2 (4%)	3 (6%)	2 (4%)	0.8608

Following adverse events like hypotension, bradycardia, shivering, postoperative nausea and vomiting were studied and analysed (chi-square test).Regarding hypotension in Group A, 3 patients (6.00%) had hypotension, Group B,2 patients(4%) had hypotension, Group C 2 patients (4%) had hypotension. Association of hypotension in these three groups were not statistically significant *(p value*-0.8608).

Incidence of Bradycardia was observed same in Group A and Group B [1patients (2.00%)] . In Group C 50 patients (100%) had no bradycardia. Association of Bradycardia in these three groups were not statistically significant *(p value*-0.6024).

Incidence of Shivering was observed same in Group A and Group C [1patients (2.00%) each group]. In Group B 50 patients (100%) had no shivering.Association of shivering in these three groups were not statistically significant *(p value*-0.6024).

Incidence of post-operative nausea & vomitingobserved same in Group A and Group C[2patients (4.00%) each group]. In Group B 3 patients (6%) had nausea & vomiting. Association of nausea & vomiting in these three groups were not statistically significant *(p value*-0.8608).

Discussion

Unilateral spinal anaesthesia is commonly used for unilateral lower limb surgeries because of its reliability,provision of excellent surgical anaesthesia and prolonged post-operative analgesia. The term unilateral spinal anaesthesia is used when the block is of operative side only with absence of block on non-operative side[6].

Use of different adjuvants along with local anaesthetic agent prolongs the duration of spinal anaesthesia with minimal side effects[7]. The co-administration of adjuvants reduce the dose requirement of local anaesthetic, increase the motor block sparing effect with better quality of analgesia. In our study with 150 consenting adult patients posted for elective lower limb surgery (duration of less than 2 hrs.) conducted at Medical College were randomly allocated into 3 groups. Gr A(30 microgram clonidine), Gr B (25 microgram Fentanyl) and Gr C(0.5 ml normal saline) with 1.5 ml 0.5% hyperbaric bupivacaine prepared to total amount of 2 ml of intrathecal drug for unilateral spinal anaesthesia in each group. The onset, duration of motor and sensory block were compared in 3 groups along with the time of requirement of the first dose of rescue analgesic thus recorded analysed and studied.We have included the patients with successful unilateral spinal anaesthesia by application of some exclusion criteria. The patients with motor power > 2 with sensory block higher than L1 in non-operative limb and patients with total failure of block had been excluded from the study.With the addition of adjuvant namely 30 microgram of Clonidine and 25 microgram Fentanyl,the onset of sensory and motor block was not significantly altered. There was prolongation of sensory and motor block seen with the use of both the adjuvants. In Gr A duration of sensory block 140±7(in minute), in Gr B is 124±7(in minute) and in Gr C is 110±9 (minute).There is statistically significant prolongation of sensory block with Clonidine compared to Fentanyl group.

There is also some prolongation of motor block with both the adjuvants and clonidine group demonstrated statistically significant prolongation of motor block compared to Fentanyl group.

Coadministration of Fentanyl and Clonidine produce significant prolongation of duration of the post-operative analgesia thus delaying the requirement of the first dose if rescue analgesic. The time duration post operatively before the requirement of the first rescue analgesic is significantly more in Clonidine (356.1400 ± 12.9379 minutes) compared to Fentanyl group (309.3600 ± 17.5252 minutes).

Fentanyl is a semisynthetic short acting lipophilic opioid that stimulates mu receptor and potentiates afferent sensory blockade and facilitates reduction in the dose of local anaesthetic without intensifying the motor block and prolonging recovery[8].

Clonidine is alpha 2 agonist used as an adjuvant with bupivacaine.During spinal anaesthesia clonidine acts by stimulating the alpha 2 receptor in substantia gelatinosa of dorsal horn that inhibits the nociceptive neurones of Adelta and C fibres and thus produces analgesia.They also decreases the release of substance P. The site of action of either Fentanyl or Clonidine in spinal cord is different from the site of action of local anaesthetic so there is synergistic action of the adjuvant which thereby prolongs the sensory and motor block of the local anaesthetic.The mechanism of prolongation of motor block is not clearly known but probably it is due to direct inhibition of impulse conduction in motor nerve fibres. Main advantage of unilateral spinal anaesthesia is stable haemodynamic status. In concordance with the previous studies[9,10] no significant fall in heart rate and blood pressure was noted. Less hypotension is probably due to less quantity of intrathecal drug required for anaesthesia, the slow ascent of the drug and unilaterality of block[11].The simultaneous factors for unilateral spinal anaesthesia are lateral decubitus position during and subsequently after intrathecal injection, low dose of local anaesthetic and slow speed of injection. Position of the patient(lateral decubitus), baricity of local anaesthetic and duration of lateral position after intrathecal injection are main characteristic of spinal block to one side[12,13].

The optimum duration of lateral decubitus for unilateral spinal anaesthesia is different to define and probably depends on the dose of local anaesthetic. With use of 7.5 mg of hyperbaric bupivacaine, the maintenance of lateral decubitus for 10 to 15 min is considered optimal[14]. As we used hyperbaric bupivacaine we positioned the patient in lateral position with operative side in dependant position and maintained this position for 10 minutes after spinal injection .Slow speed of injection minimized mixing local anaesthetic with cerebrospinal fluid (CSF) and thus facilitates unilateral block[15].

There may be several potential benefits of the daily practice of unilateral spinal anaesthesia but there are also shortcomings of the same. Placing the patients in lateral position for 10 minutes may be time consuming for a busy operation theatre. Lying on the operative side with the painful fracture is nearly distressing for patients and sometimes even impossible. Although the use of hypobaric or plain solution may increase patient acceptability in such situations, hyperbaric solutions are better for producing unilateral block.

The results of our study shows that alpha 2 adrenoceptor agonist like Clonidine can be a suitable alternative to opioid as adjuvant to local anaesthetic in unilateral spinal anaesthesia. Clonidine prolongs the duration of motor and sensory block and the time duration of need of postoperative first dose of rescue analgesic. Unilateral spinal anaesthesia is beneficial since it ensures haemodynamic stability[16] and thus hypotension, bradycardia and other significant adverse effects can be avoided. Hence Clonidine can be considered as an excellent option for adjuvant to local anaesthetic agent in unilateral spinal anaesthesia for lower limb surgery.

The obvious limitation of this study is that this study has been done in one medical college in controlled atmosphere with younger population and with relatively less cardiovascular and other comorbidities.

Conclusion

In our study with 150 consenting adults posted for elective lower limb surgery of duration ≤ 2 hours were randomly allocated into three groups with Gr A(30 microgram clonidine),Gr B (25 microgram Fentanyl) and Gr C(0.5 ml normal saline) with 1.5 ml of 0.5% hyperbaric bupivacaine prepared to amount 2 ml of intrathecal drug used for unilateral spinal anaesthesia in each group. With both Clonidine and Fentanyl in their respective doses prolonged the duration of sensory and motor block compared to the only local anaesthetic agent. Clonidine caused statistically significant prolongation compared to Fentanyl group. Clonidine can be considered as an excellent option for adjuvant to local anaesthetic agent in unilateral spinal anaesthesia for lower limb surgery. Hemodynamic parameters were maintained throughout the surgery. There was no significant incidence of other adverse effects like nausea, vomiting, pruritus or sedation in either the groups.

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