

A comparison of intrathecal dexmedetomidine and fentanyl as an adjuvant to isobaric levobupivacaine for lower limb orthopaedic surgery

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Received: 6th March, 2018

Accepted: 6th May, 2019

Abstract

Introduction: Levobupivacaine is cardiostable. Fentanyl and dexmedetomidine as adjuvant to improve quality of block.

Aim: To compare the efficacy and safety of 25 mcg of fentanyl vs 5 mcg dexmedetomidine as an adjuvant in 0.5% of 3ml of isobaric levobupivacaine in lower limb orthopaedic surgery.

Objectives: Onset and duration of sensory block, maximum sensory block. Onset and duration of motor block, maximum motor block, time to regress sensory and motor block, postoperative analgesia. Level of sedation, hemodynamic changes, side effects.

Materials and Methods

Group A: 0.5% isobaric levobupivacaine 3ml +0.5 ml of NS =3.5ml.

Group F: 0.5% isobaric levobupivacaine 3ml+25 mcg fentanyl diluted with NS =3.5ml.

Group D: 0.5% isobaric levobupivacaine 3ml + 5 mcg dexmedetomidine diluted with NS =3.5ml.

Subarachnoid block were achieved in L3-L4 interspaces. Parameters like pulse, SBP, DBP, MAP, SPO2, RR, level of sensory block, grade of motor block, sedation scale were recorded every min for 5 min, every 5 min till 30 min, every 15 min till 2 hr, every 30 min till end of surgery. Intraoperatively side effects were recorded and treated. In postoperative period total analgesic, antiemetic requirement, sedation scale checked.

Result: onset of sensory block was earlier in group F. maximum sensory block was in group D. Motor block regress faster in group A. postoperative analgesia was more in group D and side effects were less.

Conclusion: Dexmedetomidine group has longer onset of and duration of sensory block and effective postoperative analgesia and fewer side effect as compared to fentanyl group.

Keywords: Subarachnoid block, Levobupivacaine.

Introduction

Spinal anesthesia is the most commonly used technique for lower limb orthopaedic surgeries as it is very economical and easy to administer. However, postoperative pain control is a major problem because spinal anesthesia using only local anesthetics is associated with relatively short duration of action, and thus early analgesic intervention is needed in the postoperative period. A number of adjuvants, such as Clonidine and Midazolam, and others have been studied to prolong the effect of spinal anesthesia.¹

Levobupivacaine causes less cardiovascular and neurological events.

Onset of sensory and motor block is hastened with Hyperbaric Levobupivacaine compared to Isobaric Levobupivacaine.

Increased protein binding and higher clearance explains cardiostability of Levobupivacaine.²

Regression of motor block occur earlier with Levobupivacaine as compared to Bupivacaine. A common problem during lower limb orthopaedic surgeries under spinal anesthesia is post operative pain intrathecally opioids act synergistically with local anaesthetics.¹ They improve the quality of intraoperative anaesthesia, permit lower doses of local anesthetics, provide faster onset of surgical block and prolong the duration of postoperative analgesia.

Nowadays, newer Phenylpiperidine compounds like fentanyl and sufentanil are being increasingly used to provide segmental analgesia. Being highly lipid soluble and having higher affinity for opioid receptors, these drugs provide quicker onset of the block, improve the quality of intraoperative anaesthesia and prolong postoperative analgesia with fewer side effects.³

Dexmedetomidine, a new highly selective α_2 -agonist, is under evaluation as a neuraxial adjuvant as it provides stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia with minimal side effects.⁴

Dexmedetomidine has been approved by Food and Drug Administration (FDA) as a short-term sedative for mechanically ventilated intensive care unit (ICU) patients. Based on earlier human studies, it is hypothesized that intrathecal 5 μ g dexmedetomidine would produce prolong postoperative analgesic effect with Hyperbaric Levobupivacaine in spinal anaesthesia with minimal side effect.⁴⁻⁷

In this study we propose to compare a combination of isobaric Levobupivacaine with fentanyl and dexmedetomidine for the characteristics of spinal blockade with respect to onset, duration and hemodynamic parameters and side effect.

Materials and Methods

Study was carried out in department of anesthesia at our institute from November 2015 to September 2017 after ethical committee approval.

This was a prospective, randomized, and double blinded clinical comparative study to evaluate the effect, hemodynamic stability and adverse effects of using intrathecal dexmedetomidine and fentanyl as an adjuvant to Isobaric Levobupivacaine for lower limb orthopaedic surgery. The study participants were randomly divided into three groups.

Randomization was done by computer generated randomization table and allocated to one of the three study groups. In order to determine the sample for the proposed study, data published by Mahendru V. et al. (2013) was used. The authors reported various parameters like: time of onset of block, onset of motor block, duration of sensory block, duration of motor block and duration of spinal anaesthesia. In the proposed study, three groups have been considered with Saline, fentanyl and dexmedetomidine as adjuvants with the anaesthetic drug.

The effect size was estimated using the expression

$$ES = \sqrt{\frac{\sum_{i=1}^k di^2}{k}}$$

where

$$di = \frac{xi - \bar{x}}{s}$$

Where for $i=1,2,3\dots k$, and xi is the mean for i^{th} group, is the mean of three groups. Accordingly, the effect size for the study parameters were obtained which ranged between 0.196 to 0.905. An effect size of 0.3 was set, which resulted into a sample size of 111 (~120) cases. In other words, a samples of 40 per group can provide significant difference in the parameters of interest especially duration of sensor block, motor block with 95% confidence and 80% power. The data generated on the cases for various study parameters analysed statistically using appropriate parametric tests like t-test, ANOVA etc. and the significance tested at 5%. The computations was performed using SPSS 18.0 (SPSS Inc.) tool.

The study population consisted of one twenty adult patients who were classified as American Society of Anesthesiologists (ASA) physical status I or II, undergoing

Modified Bromage Scale

Grade	Criteria	Degree of block
O	Free movement of legs and feet.	Nil (0%)
I	Knee flexion decrease but full flexion of feet and ankle	Partial (33%)
II	Unable to flex knees, flexion of ankle and feet present	Partial (66%)
III	Unable to flex knee or ankle or move toes	Complete paralysis (100%)

Sedation is assessed by the Ramsay sedation scale.

elective lower limb orthopaedic surgery under spinal anaesthesia.

Inclusion Criteria

1. Patient aged between 18 to 60yrs of either sex.
2. ASA 1 and 2
3. Patient posted for elective lower limb orthopaedic surgeries.
4. Height 150-180 cm.
5. Weight 50-70 kg.

Exclusion Criteria

1. History of allergy to study drugs.
2. Patient refusal.
3. Patients using alpha 2-adrenergic receptors antagonists, calcium channel blockers, angiotensin-converting enzyme inhibitor.
4. Patient having absolute contraindication to spinal anaesthesia.

Careful pre anaesthetic check-up was carried out in all patients with detailed clinical history, general and systemic examination. After checking the informed consent overnight fasting for 8-10hrs done. All patients were preloaded with Ringer lactate solution 10ml/kg over 15 minutes before the spinal anaesthesia. The base line heart rates, systolic, diastolic and mean Blood pressure, SpO2 respiratory rate, were recorded. Then after Subarachnoid Block, all the parameters like pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SPO2, respiratory rate, level of sensory block, grade of motor block, sedation scale at every 1 minute for 5 minutes; then every 5 minutes till 30 minutes and then every 15 min upto 2 hrs and then after every 30 min till the end of surgery. In the postoperative period following parameters are observed pulse, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SPO2, VAS, 1st rescue analgesic requirement, total analgesic requirement in 24 hr period, sedation scale and side effect were recorded immediately in postoperative recovery room, 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 8 hr, 12 hr, 18 hr, 24 hr period.

Group A: 0.5% Levobupivacaine Isobaric 2.5ml+ 0.5ml normal saline (total volume is upto 3.0 ml).

Group F: 0.5% Levobupivacaine Isobaric 2.5ml + 25mcg fentanyl (test solution will diluted with normal saline to total volume of 3.0ml).

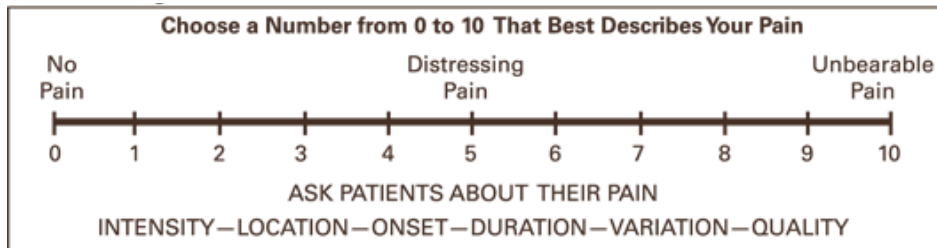
Group D: 0.5% Levobupivacaine isobaric 2.5ml +5 mcg dexmedetomidine (test solution will diluted with normal saline to total volume of 3.0 ml).

Sensory anaesthesia assessed by loss of sharp sensation to pinprick test in the midclavicular line. Motor blockade was determined using Modified Bromage scale.

Ramsay Sedation Scale

1. Patient is anxious and agitated or restless, or both
2. Patient is cooperative, oriented and tranquil
3. Patient responds to commands only
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6. Patient exhibits no response

Visual Analogue Scale



Assessment of Analgesia

Pain was assessed by visual analogue scale (VAS) 1st analgesic requirement and 24 hr analgesic requirement were assessed was defined as when VAS score was more than 4. Total number of analgesic requirement. Analgesia was given by intravascular inj of paracetamol 1 gram and supplementary analgesic was given as inj diclofenac sodium 75 mg iv. Total no of doses of analgesic in 24 hr period were recorded.

Adverse Effects

Occurance of nausea, Pruritis, Shivering, drowsiness, dry mouth, bradycardia, hypotension recorded and treated.

Failure of the block denoted if sensory blockade not reach T10 level.

Result and Discussion

Table 1: Comparison of demographic parameters

Parameters	Group A	Group D	Group F	P-value
	(n=40)	(n=40)	(n=40)	
Age (years) [mean±SD]	35.45±9.84	37.28±14.39	38.60±14.39	0.533 (NS) [†]
Gender [No. (%)]				
Male	27 (67.5)	31 (77.5)	27 (67.5)	0.525 (NS)*
Female	13 (32.5)	9 (22.5)	13 (32.5)	
ASA				
1	38 (95.0)	36 (90.0)	36 (90.0)	0.646 (NS)*
2	2 (5.0)	4 (10.0)	4 (10.0)	
weight (mean ±SD)	63.70±2.75	63.28±1.61	63.93±2.05	0.407 (NS)
Height (mean ±SD)	159.20±2.69	159.78±2.93	159.15±3.08	0.566 (NS)
duration of surgery (mean ±SD)	91.37±16.83	97.88±18.28	99.38±13.02	0.068 (NS)

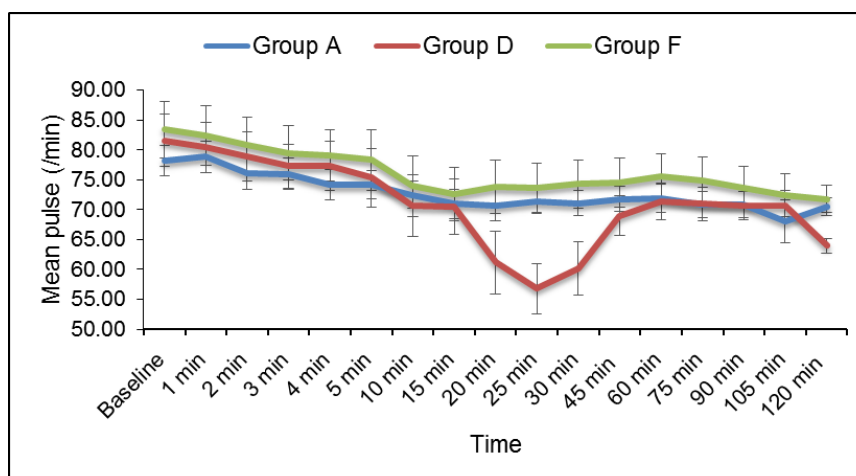


Fig. 1: Line diagram showing mean pulse according to time points for three treatment groups in the intraoperative period

*Obtained using ANOVA; S: Significant; NS: Not Significant; [†]First significant drop compared to baseline

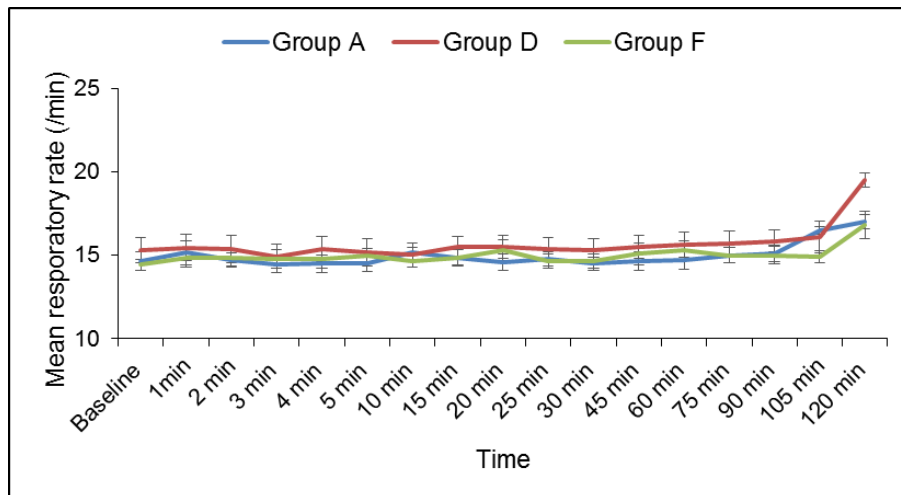


Fig. 2: Line diagram showing mean respiratory rate according to time points in three treatment groups in intraoperative period

*Obtained using ANOVA; S: Significant; NS: Not Significant; ‡ First significant drop compared to baseline

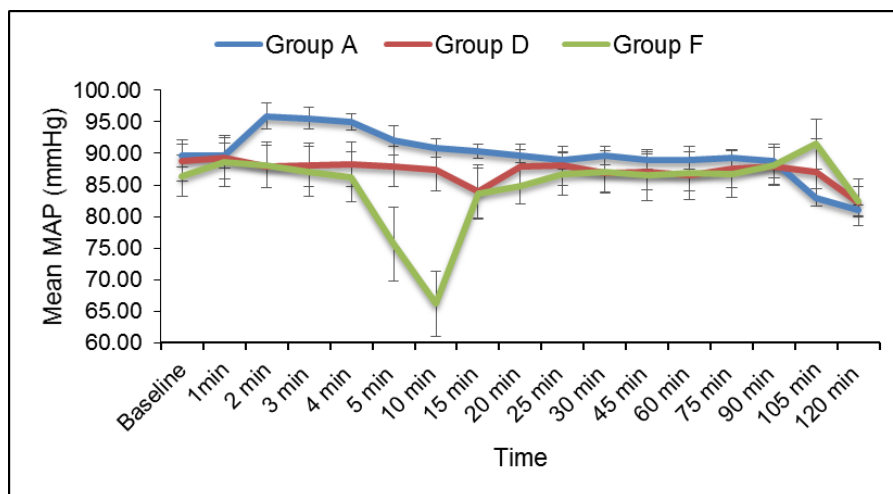


Fig. 3: Line diagram showing mean arterial pressure according to time points in three treatment groups

*Obtained using ANOVA; S: Significant; NS: Not Significant; ‡ First significant drop compared to baseline

Table 2: Comparison of Sensory and Motor block parameters across three groups

Parameters	Mean ± SD						P-value
	Group A		Group D		Group F		
	(n=40)	(n=40)	(n=40)	(n=40)	(n=40)	(n=40)	
Onset of sensory block (in min)	10.70	3.93	8.25	2.89	2.10	1.15	< 0.001* (S)
Duration of sensory block (in min)	112.28	7.01	203.28	6.36	159.00	12.69	< 0.001* (S)
Onset of motor block (in min)	10.95	4.03	9.00	3.24	3.23	1.25	< 0.001* (S)
Duration of motor block (in min)	157.45	6.30	250.20	6.52	184.25	11.73	< 0.001* (S)
Time taken to achieve for maximum sensory block (in min)	15.55	4.86	13.25	3.49	5.33	1.85	< 0.001* (S)
Bromage Scale	[No. (%)]						
3: Inability to raise leg, flex knee or ankle or move toes	40	100	40	100	40	100	< 0.001† (S)

*Obtained using ANOVA; † Obtained using Chi-square test; S: Significant;

Table 2 provides the descriptive statistics like mean and SD for sensory and motor block parameters for each group with p value <0.001

Table 3: Comparison of maximum sensory block attained in three groups

Maximum sensory block attained	Group A (n=40)	Group D (n=40)	Group F (n=40)	P-value*
T4 dense	0	0	2 (5.0)	< 0.001 (S)
T6 dense	0	6 (15.0)	29 (72.5)	
T8 dense	5 (12.5)	20 (50.0)	9 (22.5)	
T10 dense	35 (87.5)	14 (35.0)	0	

*Obtained using *Chi square test*; S: Significant

Table 3 provides the comparison for maximum sensory block attained in three groups. Showed statistically significant difference across three groups as indicated p-value of <0.001.

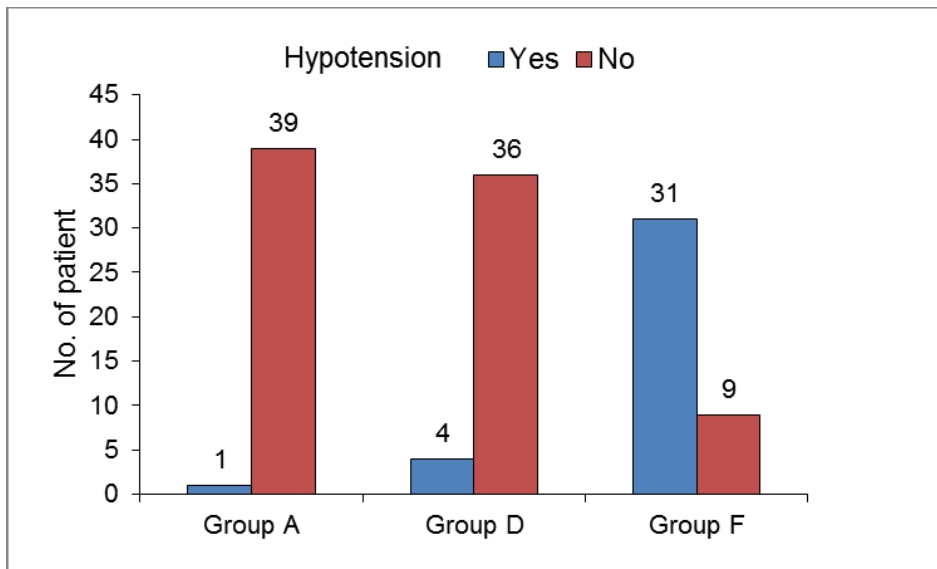


Fig. 4: Bar chart showing number of patients according to hypotension in three treatment groups

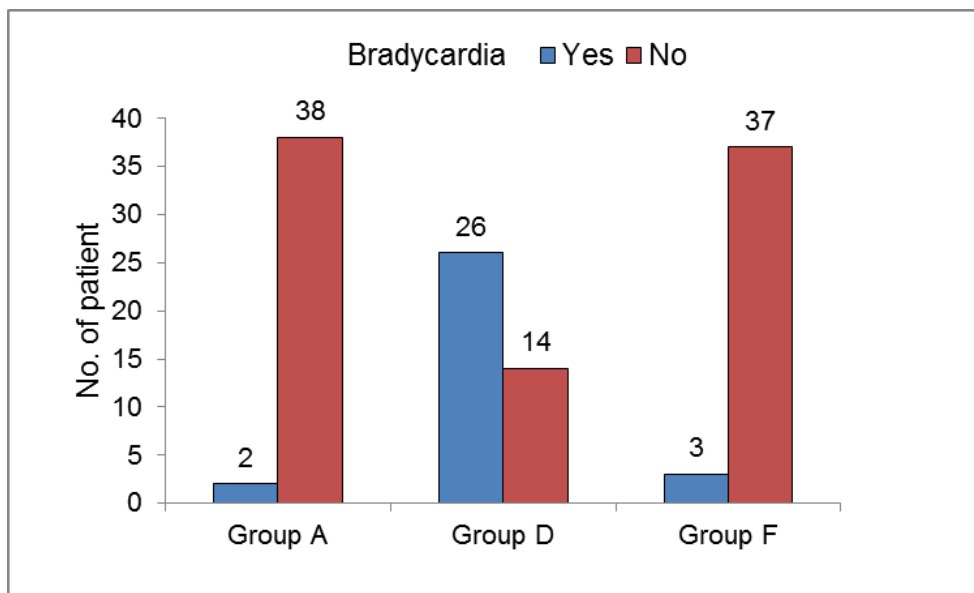


Fig. 5: Bar chart showing number of patients according to bradycardia in three treatment groups

Table 4: Frequency distribution according to first analgesic requirement in patients – Post operative period

Post-operative first analgesic requirement	No. (%)
Group A	
Intraoperative	16(40)
Postoperative recovery	12(30.0)
0.5hr	12 (30.0)
Group D	
2 hr	1 (2.5)
3 hr	7 (17.5)
4 hr	21 (52.5)
6 hr	11 (27.5)
Group F	
Postoperative recovery room	4(10.0)
0.5 hr	18(45.0)
1 hr	14 (35.0)
2 hr	4 (10.0)

Table 5: Frequency distribution according to total analgesic requirement in 24 hr – Postoperative period

Group / Number of doses in 24 hr.	No. (%)
Group A	
4	15 (37.5)
5	21 (52.5)
6	4 (10.0)
Group D	
1	3 (7.5)
2	36 (90.0)
3	1 (2.5)
Group F	
1	1 (2.5)
2	8 (20.0)
3	31 (77.5)

Discussion

In this study we compared the 5 mcg dose of dexmedetomidine with 25 mcg dose of fentanyl administered to the Isobaric Levobupivacaine. There were very few studies that compared both the doses simultaneously with Isobaric Levobupivacaine; we have compared and discussed our results with various other studies using similar adjuvants in same doses but in combination with various local anaesthetic as well in various surgeries. The values of the demographic variables were comparable between the three groups.

Onset of sensory block defined as time taken to attain the T12 dermatomal level. Our study showed mean time for onset of sensory block was 10.70 ±3.93 min in the saline group and 8.25±2.89 min in the dexmedetomidine group and 2.10±1.15 min in the fentanyl group. So onset of sensory block occurred earlier in the fentanyl group. Mohamad Kamal et al in 2017⁸ found that the onset of sensory block was 3.22±0.69 min in the group F and 3.90±0.94 min in the group D with p value highly significant p <0.001. Shelly Rana⁹ in 2017 stated that the earlier onset with fentanyl can be attributed to its lipophilic

properties. The lipophilic opioids rapidly traverse the dura mater, where they are sequestered in the epidural fat and enter the systemic circulation; they also rapidly penetrate the spinal cord where they binds opioid receptors within the white matter as well as dorsal horn receptors and eventually enter the systemic circulation as they are cleared from the spinal cord. Al Ghanem et al 2009⁵ found the onset time for sensory block was upto T10 level and it was 7.5±7.4 min in dexmedetomidine group and 7.4±3.3 min in fentanyl.

The mean time taken to achieve maximum sensory block in group A was 15.55±4.86 min, in group D was 13.25±3.49 min and in group F it was 5.33±1 min so maximum sensory block was achieved earlier in group F. Nayagam HA et al (2014)¹⁰ found that the mean time for peak sensory levels was (11.88 ± 2.156) min in fentanyl group and in dexmedetomidine group it was (12.92 ± 3.131) min. The difference between the two means was statistically significant. (p<0.05). Al Ghanem et al in 2009⁵ studied and found that time to reach the maximum sensory block was around 19.34±2.87 min in the dexmedetomidine group and 18.39±2.46 min in the fentanyl group which was statistically insignificant with p value of 0.12.

Peak level of sensory block attained in the fentanyl group was T4 and the peak level of sensory block in dexmedetomidine group was T6 and in the saline group peak level was T8. So the highest sensory block was attained in the fentanyl group. Curvas et al in 2010⁸⁰ found the difference in the sensory block and this can be explained by the difference in the baricity of the solutions ;opioids are hypobaric and when added to the hypobaric local anaesthetic make the mixture more hypobaric thus altering the density of the resulting solution which affect the direction and extent of spread. Al Ghanem M Subhi et al⁵ (2009) found out that highest sensory level was T6 in the Dexmedetomidine group and in the fentanyl group it was around T8 level.

Mean duration of sensory block in group A was 112.28±7.01 min, and in group F was 159.00±12.69 min., and in group D was 203.28±6.36 min. Prolong duration occur in the dexmedetomidine group. The prolongation of effect may result from synergism between local anaesthetic and alpha2 adrenoceptor agonist action. Ahmed Basuni et al¹¹ in 2013 also stated the prolongation of the block in the dexmedetomidine.

In our study mean onset time of motor block in group A was 10.95±4.03 min, in group D it was 9.00±3.24 min, in group F it was 3.23 ±1.25 min. Onset of motor block occurred earlier in the fentanyl group. Mohamad Kamal et al in 2017⁸ found that onset of motor block was 3.74±0.57 min in the group F and 4.44±0.91 min in the group D with p value<0.001.

In the present study there was a significant difference in duration of motor block across the three groups with p value <0.001. In group A mean duration of motor block was 157.45±6.30 min, and in group D was 250.20±6.52 min and in group F it was 184.25±11.73 min.

Mahendru et al (2013)¹² found that duration of motor block was (161.5±19.8 min) in saline group. (196.0 ± 26.8)

min in group fentanyl and (198.7±26.4 min) in clonidine, (273.3 ± 24.6) min in the dexmedetomidine group (P <0.0001).

Dr Rayees Ahmad et al 2016¹³ found duration of motor block in the fentanyl group was around 152.90 ±8.31 min and in the dexmedetomidine group it was around 419.70±16.85 min.(p<0.001)

In the present study there was a significant difference in the pulse rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure from the 2 min to 20 min in the intraoperative period.

In the postoperative time period the pulse rate, systolic blood pressure, diastolic blood pressure, mean blood pressure was not statistically significant with p value of >0.05.

Khan A L et al (2015)¹⁴ inferred that the heart rate at all intervals was lower in dexmedetomidine group when compared to fentanyl group.

Rao et.al in 2015¹⁵ found that the significant decrease in the pulse rate was observed in the dexmedetomidine group as compared to the fentanyl and control.

Ahmed Sobhy Basuni et al (2013)¹¹ found that blood pressure was comparable in the two groups throughout the surgery. 2 patients in group F showed intraoperative period hypotension.

Mohamad Kamal et al in 2017⁸ stated that hypotension occur in both the groups but the value was not statistically significant in using the intravenous vasopressor therapy.

Mechanism of sedation in the dexmedetomidine group is due to action on the sleep promoting pathway. In the present study both intraoperative and postoperative period dexmedetomidine contribute to sedation scale 2. Rajani Gupta R et al (2011)¹ stated that the mean sedation score was (3.8±0.5) in group dexmedetomidine as compared to (2.2±0.53) in group fentanyl (P<0.05).

Rayees Ahmad R et al (2016)¹³ found the mean sedation score for group dexmedetomidine was (3.40 ± 0.49) and in fentanyl was (2.16 ± 0.37), (P <0.001).

There was no significant difference between the three groups in the respiratory rate.

Similar to Ahmed Sobhy Basuni et al in 2013¹¹ and R. Ahmed et.al in 2009.¹³

In regard, first analgesic requirement was prolonged in group D as compared to group A and group F and requirement of 24 hr analgesia was also found lower in the dexmedetomidine group, and however supplementary analgesia in the form of diclofenac 75 mg iv was required in group A only.

Aamir Laique Khan et.al in 2015¹⁴ studied that the time for first analgesic requirement in the dexmedetomidine group was (280±7.84) min and in the fentanyl group it was (173.88±8.12) min after the starting of surgery which was highly significant with p value of (<0.001).

Farhad Safari, et al in 2016¹⁶ Total morphine doses in 24 hours was significantly lower in the dexmedetomidine group as compared to fentanyl and control groups (P < 0.05).

Ayman Eskander et al in 2017¹⁷ found that the postoperative analgesic requirement in first 24 hr was significantly lower in the dexmedetomidine and the fentanyl group compared to the control group and it was significantly lower in the dexmedetomidine group than fentanyl group (p < 0.05).

In the present study no patient had episode of respiratory depression.

Vidhi Mahendru et al in 2013,¹² Rajani Gupta et al 2011¹ in both the studies there was no evidence of respiratory depression.

In the present study no patient in any of the groups had side effects like shivering, pruritus, nausea vomiting, similar to Ahmed Sobhy Basuni et al 2013.¹¹

Al Ghanem et al in 2009⁵ stated that that 2 (5%) patients in the dexmedetomidine group and 4(10%) patients in the Fentanyl group had nausea and vomiting with p value of 0.401, no patient in the dexmedetomidine group got pruritus and 5 patients in the fentanyl group had pruritus.

Gupta R et al (2011)¹ studied intrathecally dexmedetomidine and fentanyl as adjuvant to Bupivacaine in lower abdominal surgeries. In group dexmedetomidine only one patient had Nausea and no patient had vomiting while in group fentanyl two patients had nausea and one patient had vomiting. One patient in the fentanyl group had pruritus.

In the present study 26 (65%) patient in the dexmedetomidine group had bradycardia while in the fentanyl group 3(7.5%) patients and in the saline group 2 (5%) patients had bradycardia being statistically significant.

However there was no episode of bradycardia found in Ahmed Sobhy Basuni et al¹¹ in 2013 and Mohamad Kamal et al in 2017⁸ studies.

Ghanem et al in 2009⁵ stated that side effect of bradycardia was less because small dose of intrathecal dexmedetomidine was used in their study.

In our study, 31 patients in the fentanyl group had episode of hypotension. Which was treated with inj mephentermine 3 mg in incremental doses.

The maximum hypotension occur in the F Ahmad R et al (2016)¹³ studied they found that 14(28.0%) patients in group fentanyl and 8 (16.0%) patients in group dexmedetomidine had hypotension, Al Ghanem M Subhi et al⁵ (2009) found that four patients (10%) in group dexmedetomidine and nine patients(24%) in group fentanyl developed hypotension, and the di

Limitations of Present Study

1. Our study was done on patients age groups of 18 to 60 years of age with ASA
2. Physical Status I and II only. Hence results may not be extrapolated to ASA Physical Status III & IV patients. Further studies are required to investigate the efficacy of dexmedetomidine in ASA III and IV and medically compromised patients also.
3. Similar studies with decreased Intrathecal dose of dexmedetomidine with Isobaric Levobupivacaine in SAB so as to reduce the duration of motor blockade

may be targeted. We have not compared the systemic effect of adjuvant.

Conclusion

1. On the basis of observations made, the following conclusions can be drawn:
2. Onset of sensory blockade was significantly faster in fentanyl group as compared to dexmedetomidine group.
3. Mean duration of sensory and motor block was significantly longer in dexmedetomidine group as compared to fentanyl group.
4. Dexmedetomidine and fentanyl groups showed significant difference in the heart rate and Blood Pressure (SBP, DBP and MAP) throughout the, intra-operative period, in the postoperative period there was no significant difference.
5. Incidence of Bradycardia was higher in the dexmedetomidine group and hypotension was maximum in fentanyl group as compared to dexmedetomidine group.
6. Incidence of Nausea, vomiting and Pruritus, respiratory depression, shivering not occur in the any of the group to conclude, 5 µg dexmedetomidine is effective as adjuvant to Isobaric.

Levobupivacaine in prolonged duration of sensory and motor blockade, good hemodynamic stability with decreased incidence of side effect but onset of sensory and motor block occur earlier in the fentanyl group

So as compared to 25 mcg fentanyl. 5 µg of dexmedetomidine may be used as alternative adjuvant to intrathecal Isobaric Levobupivacaine in elective lower limb orthopaedic surgery hence, dexmedetomidine seems to be an attractive alternative as Intrathecal adjuvant with Levobupivacaine when compared with fentanyl.

Conflict of Interest: None.

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How to cite this article: Bhure A, Jagtap N. A comparison of intrathecal dexmedetomidine and fentanyl as an adjuvant to isobaric levobupivacaine for lower limb orthopaedic surgery. *Indian J Clin Anaesth* 2019;6(1):89-96.