ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2021; 13(5); 315-323

Original Research Article

A Study Comparing Intrathecal Dexmedetomidine and Fentanyl as Adjuvants to Isobaric Levobupivacaine for Lower Limb Orthopaedic Surgery: Double Blinded Clinical Trial

Shashi Bhushan Sinha

Professor, Department of Anaesthesia, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar, India

Received: 29-08-2021 / Revised: 11-09-2021 / Accepted: 27-09-2021
Corresponding author: Dr. Shashi Bhushan Sinha
Conflict of interest: Nil

Abstract

Aim: The aim of the study 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. **Methods:** This was a prospective, randomized, and double blinded clinical comparative study conducted in the Department of Anaesthesia, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar, India. The study population consisted of 300 adult patients who were classified as American Society of Anesthesiologists (ASA) physical status I or II, undergoing elective lower limb orthopaedic surgery under spinal anesthesia. The study participants were randomly divided into three groups. Group A: 0.5% Levobupivacaine Isobaric 2.5ml+ 0.5ml normal saline (total volume is up to 3.0 ml). Group F: 0.5% Levobupivacaine Isobaric 2.5ml + 25mug 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. **Result:** The mean time for onset of sensory block was 12.04 ±4.21 min in the saline group and 9.76±2.99 min in the dexmedetomidine group and 3.28±1.42 min in the fentanyl group. The mean time taken to achieve maximum sensory block in group A was 17.18±4.83 min, in group D was 15.16±3.42 min and in group F it was 6.52±1.67 min so maximum sensory block was achieved earlier in group. 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. The mean duration of sensory block in group A was 116.63±7.15min, and in group F was 164.32±12.74min., and in group D was 207.17±6.42 min. Prolong duration occur in the dexmedetomiine group. The prolongation of effect may result from synergism between local anaesthetic and alpha2 adrenoceptor agonist action. The mean onset time of motor block in group A was 12.04±4.21 min, in group D it was 9.76±2.99 min, in group F it was 3.28 ±1.42 min. Onset of motor block occured earlier in the fentanyl group. 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 162.04±6.42 min, and in group D was 254.29±6.62 min and in group F it was 187.88±11.16 min. 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. **Conclusion:** Dexmedetomidine group has longer onset of and duration of sensory block and effective postoperative analgesia and fewer side effects as compared to fentanyl group.

Keywords: Subarachanoid block, Levobupivacaine.

Introduction

Spinal anesthesia is still the first choice for cesarean section due to its deep sensory block as well as fewer side effects on mother and fetus[1,2]. Despite many benefits of this method, it has a short duration and cannot provide sufficient postoperative analgesia. Adequate postoperative analgesia plays a crucial role in cesarean delivery because it allows better breastfeeding and caring for newborns. Nowadays, many drugs including opioids, magnesium sulphate, vasopressors, and α2-adrenergic agonists (dexmedetomidine and clonidine) have been tried extensively as an adjuvant to local anesthetic and provide some advantages not only to manage postoperative pain but also to optimize satisfaction of patients[2-4].

Fentanyl is the most common short-acting opioid that is used intrathecally in combination with local anesthetics. It has synergistic effects with local anesthetics and improves the status of intraoperative and postoperative analgesia[3]. It has been reported that intrathecal administration of fentanyl at the dose of 10–25 microgram can prolong the duration of postoperative analgesia for approximately 180–240 min[5]. However, intrathecal opioids can cause some side effects such as itching, urinary retention, nausea and vomiting as well as respiratory depression[6,7]. Dexmedetomidine (Dex), a new selective α2-agonist, is being introduced as an adjuvant to local anesthetics with significant analgesic, sympatholytic and sedative properties[2,6,8]. Compared to clonidine; Dex is approximately eight times more selective towards α2-adrenergic receptors (α2-AR), which is associated with sedative and analgesic effects in supraspinal and spinal sites and also has an antinociceptive impact on both visceral and somatic pain. More importantly, this drug does not cross the placenta significantly (0.77 maternal/fetal index), which confirmed its safety in cesarean delivery[9]. Many reports have indicated that intrathecal administration of Dex can prolong analgesia and reduce the side effects associated with the administration of opioids[2,6,8,10]. However, some studies have reported that intrathecal injection of Dex is frequently associated with some side effects, such as a decrease in heart rate and blood pressure[10-12].

Materials and methods

This was a prospective, randomized, and double blinded clinical comparative study conducted in the Department of Anaesthesia, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar, India after taking the approval of the protocol review committee and institutional ethics committee. We evaluate the effect, hemodynamic stability and adverse effects of using intrathecal dexmedetomidine and fentanyl as an adjuvant to Isobaric Levobipivacaine for lower limb orthopaedic surgery. The study participants were randomly divided into three groups. The study population consisted of 300 adult patients who were classified as American Society of Anesthesiologists (ASA) physical status I or II, undergoing elective lower limb orthopaedic surgery under spinal anesthesia. 300 patients with age between 20 to 60 yrs of sex, ASA 1 and 2 and patient posted for elective lower limb orthopaedic surgeries were include in this study. Patients who had History of allergy

to study drugs and Patients using alpha 2-adrenergic receptors antagonists, calcium channel blockers, angiotensin-converting enzyme inhibitor were exclude from the study.

Methodology

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, SpO_2 respiratory rate, were recorded. Then after Subarachnoid Block, all the parameters like pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SPO_2, 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 up to 2 hrs and then after every 30 min till the end of surgery. In the postoperative period following paramerters are observed pulse, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SPO_2, 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 + 25mug 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 anesthesia assessed by loss of sharp sensation to pinprick test in the midclavicular line. Motor blockade was determined using Modified Bromage scale.

Result

The mean time for onset of sensory block was 12.04 ±4.21 min in the saline group and 9.76±2.99 min in the dexmedetomidine group and 3.28±1.42 min in the fentanyl group. The mean time taken to achieve maximum sensory block in group A was 17.18±4.83 min, in group D was 15.16±3.42 min and in group F it was 6.52±1.67 min so maximum sensory block was achieved earlier in group. 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. The mean duration of sensory block in group A was 116.63±7.15min, and in group F was 164.32±12.74 minutes and in group D was 207.17±6.42 minutes. Prolong duration occur in the dexmedetomiine group. The prolongation of effect may result from synergism between local anaesthetic and alpha2 adrenoceptor agonist action. The mean onset time of motor block in group A was 12.04±4.21 min, in group D it was 9.76±2.99 min, in group F it was 3.28 ±1.42 min. Onset of motor block occurred earlier in the fentanyl group. 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 162.04±6.42 min, and in group D was 254.29±6.62 min and in group F it was 187.88±11.16 min. 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. 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. No patient in any of the groups had side effects like shivering, pruritus, nausea vomiting, and no patient had episode of respiratory depression. There were 62 (62%) patients in the dexmedetomidine group had bradycardia while in the fentanyl group 7(7%) patients and in the saline group 6 (6%) patients had bradycardia being statistically significant.

Table 1: Comparison of demographic parameters

Parameters	Group A (n=100)	Group D (n=100	Group F (n=100	P-value
Age (years) [mean±SD]	37.01±8.21	38.09±13.03	37.19±13.28	0.51 (NS)
Gender [No. (%)]				
Male	67(67)	75 (75)	64(64)	0.52(NS)
Female	33 (33)	25(25)	36(36)	
ASA				
1	93(93)	88 (88)	87 (87)	0.62 (NS)
2	7 (7)	12(12)	13(13)	
weight (mean ±SD)	66.29±2.59	66.32±1.64	66.98±2.02	0.46(NS)
Height (mean ±SD)	162.12±2.51	162.71±2.74	162.09±3.08	0.54 (NS)
duration of surgery (mean ±SD)	91.87±16.55	100.36±18.42	101.27±13.26	0.07 (NS)

*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 (n=100)		Group D (n=100		Group F (n=100)		
Onset of sensory block (in min)	12.04	4.21	9.76	2.99	3.28	1.42	< 0.001 (S)
Duration of sensory block (in min)	116.63	7.15	207.17	6.42	164.32	12.74	< 0.001 (S)
Onset of motor block (in min)	12.21	3.77	9.89	3.64	4.55	1.39	< 0.001 (S)
Duration of motor block (in min)	162.04	6.42	254.29	6.62	187.88	11.16	< 0.001 (S)
Time taken to achieve for maximum sensory block (in min)	17.18	4.83	15.16	3.42	6.52	1.67	< 0.001 (S)
Bromage Scale	No. (%)						
Inability to raise leg, flex knee or ankle or move toes	100	100	100	100	100	100	< 0.001 (S)

Obtained using ANOVA, obtained using Chi-square test; S: Significant

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

Maximum sensory block attained	Group A (n=100)	Group D (n=100)	Group F (n=100)	P-value
T4 dense	0	0	7 (7)	< 0.001 (S)
T6 dense	0	14 (14)	71 (71)	
T8 dense	20 (20)	57(57)	22 (22)	
T10 dense	80(80)	29 (29)	0	

Obtained using Chi square test; S: Significant

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

Post-operative first analgesic requirement	No. (%)
Group A	
Intraoperative	44(44)
Postoperative recovery	26(26)
0.5hr	30 (30)
Group D	
2 hr	6(6)
3 hr	1 (21)
4 hr	46 (46)
6 hr	27 (27)
Group F	
Postoperative recovery room	11(11)
0.5 hr	46(46)
1 hr	33 (33)
2 hr	10 (10)

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	34 (34)
5	51 (51)
6	15 (15)
Group D	
1	7 (7)
2	89 (89)
3	4 (4)
Group F	
1	8 (8)
2	17 (17)
3	75 (75)

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 the mean time for onset of sensory block was 12.04 ±4.21 min in the saline group and 9.76±2.99 min in the dexmedetomidine group and 3.28±1.42 min in the fentanyl group. So, onset of sensory block occurred earlier in the fentanyl group Mohamad Kamal et al in (2017)[13] found that the onset of sensory block was 4.22±0.69 min in the group F and 4.90±0.94 min in the group D with p value highly significant p <0.001. Shelly Rana (2017)[14] 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 bind 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 (2009)[15] found the onset time for sensory block was up to 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 16.18±4.83 min, in group D was 14.16±3.42 min and in group F it was 5.52±1.67 min so maximum sensory block was achieved earlier in group. Nayagam HA et al (2014)[16] 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 (2009)[15] 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 stastistically 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. Ghanem M Subhi et al (2009)[15] found out that highest sensory level was T6 in the Dexmedetomidine group and in the fentanyl group it was around T8 level. The mean duration of sensory block in group A was 116.63±7.15min, and in group F was 164.32±12.74min., and in group D was 207.17±6.42 min. Prolong duration occur in the dexmedetomiine group. Prolong duration occur in the dexmedetomiine group. The prolongation of effect may result from synergism between local anaesthetic and alpha2 adrenoceptor agonist action. Ahmed Basuni et al[17] in 2013 also stated the prolongation of the block in the dexmedetomidine.

In our study the mean onset time of motor block in group A was 12.04±4.21 min, in group D it was 9.76±2.99 min, in group F it was 3.28 ±1.42 min. Mohamad Kamal et al (2017)[13] 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 162.04±6.42 min, and in group D was 254.29±6.62 min and in group F it was 187.88±11.16 min. Mahendru et al (2013)[18] 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 (2016)[19] 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)[20] inferred that the heart rate at all intervals was lower in dexmedetomidine group when compared to fentanyl group. Rao et.al (2015)[21] 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)[17] found that blood pressure was comparable in the two groups

throughout the surgery. 3 patients in group F showed intraoperative period hypotension. Mohamad Kamal et al (2017)[13] 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)[22] 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)[19] 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 (2013) and R. Ahmed et.al in (2009)[17,19]. 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.

Khan AL et al. (2015)[20] 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).

A Safari F et al. (2016)[23] total morphine dose 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 (2017)[24] 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)[18], Rajani Gupta et al (2011)[22] 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)[17]. Al Ghanem et al in (2009)[15] 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 pruitu.

Gupta R et al (2011)[22] 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. There was 63 (63%) patients in the dexmedetomidine group had bradycardia while in the fentanyl group 7(7%) patients and in the saline group 6 (6%) patients had bradycardia being statistically significant. However, there was no episode of bradycardia found in Ahmed Sobhy Basuni et al. (2013)[17] and Mohamad Kamal et al (2017)[13] studies. Ghanem et al (2009)[15] stated that side effect of bradycardia was less because small dose of intrathecal dexmedetomidine was used in their study. In our study, 77 patients in the fentanyl group had episode of hypotension. Which was treated with inj mephentermine 3 mg in incremental doses? The maximum hypotension occurs in the F Ahmad R et al (2016)[19] studied they found that 14 (28.0%) patients in

group fentanyl and 8 (16.0%) patients in group dexmedetomidine had hypotension.

Conclusion

The present study concluded that Dexmedetomidine group has longer onset of and duration of sensory block and effective postoperative analgesia and fewer side effect as compared to fentanyl group.

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