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Double blinded clinical comparative trial of intrathecal dexmedetomidine and fentanyl as an adjuvant to isobaric levobupivacaine

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Abstract

Aim: To compare a combination of isobaric Levobupivacaine with fentanyl and dexmedetomidine.

Material and methods: This was a prospective, randomized, and double blinded clinical comparative study conducted in the Department of Anaesthesiology Metro Hospital and Cancer Research Center, Jabalpur, Madhya Pradesh, India. The study population consisted of 180 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 upto 3.0 ml). Group F: 0.5% Levobupivacaine Isobaric 2.5ml + 25µg 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 10.74 ±4.11 min in the saline group and 8.56±2.89 min in the dexmedetomidine group and 2.18±1.32 min in the fentanyl group. The mean time taken to achieve maximum sensory block in group A was 15.78±4.93 min, in group D was 13.36±3.62 min and in group F it was 5.42±1.87 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.

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: Subarachnoid block, levobupivacaine

Introduction

Spinal anesthesia is the most commonly used technique for lower abdominal 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, 2]. A common problem during lower abdominal surgeries under spinal anesthesia is visceral pain, nausea, and vomiting [3]. Some drugs have been used as adjuvants in spinal anesthesia to prolong intraoperative and postoperative analgesia including opioids, α_2 agonists, neostigmine, vasoconstrictors, etc. Clonidine and dexmedetomidine are two α_2 agonists affecting via pre- and post-synaptic α_2 receptors [4]. Dexmedetomidine has been widely used for anesthesia and analgesic purposes. This drug has sedative, anti-anxiety, analgesic, neuroprotective, and anesthetic-sparing effects [5]. Dexmedetomidine along with other drugs have been used to increase the duration of analgesia in subarachnoid, epidural and caudal blocks [6, 7]. 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 [8]. Fentanyl is a synthetic opioid with central action, which is used widely for pain control. Intrathecal fentanyl is usually added to other local anesthetics to increase anesthesia and analgesia. It has improved spinal anesthesia and reduced the anesthetic drug related side effects including pruritus, nausea and vomiting [9]. Dexmedetomidine and fentanyl have been used as adjuvant to local anesthetics in different surgeries to provide superior analgesia and to improve the

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duration of the block [10-12]. 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.

Material and Methods

This was a prospective, randomized, and double blinded clinical comparative study conducted in the Department of Anaesthesiology Metro Hospital and Cancer Research Center, Jabalpur, Madhya Pradesh, India. after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

We 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.

The study population consisted of 180 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. 180 patients with age between 20 to 60yrs of either 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.

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 up to 2hrs 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 24hr period, sedation scale and side effect were recorded immediately in postoperative recovery room, 0.5hr, 1hr, 1.5hr, 2hr, 3hr, 4hr, 8hr, 12hr, 18hr, 24hr 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 + 25µg 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 10.74±4.11 min in the saline group and 8.56±2.89 min in the dexmedetomidine group and 2.18±1.32 min in the fentanyl group. The mean time taken to achieve maximum sensory block in group A was 15.78±4.93 min, in group D was 13.36±3.62 min and in group F it was 5.42±1.87 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 114.63±7.25min, and in group F was 162.32±12.84min., and in group D was 205.17±6.52 min. Prolong duration occur in the dexmedetomidine group. The prolongation of effect may result from synergism between local anaesthetic and alpha 2 adrenoceptor agonist action. The mean onset time of motor block in group A was 11.11±3.87 min, in group D it was 8.79±3.54 min, in group F it was 3.45 ±1.29min. 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±6.52 min and in group D was 254.29±6.72 min and in group F it was 187.88±11.26 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 24hr 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 was 38 (63.33%) patient in the dexmedetomidine group had bradycardia while in the fentanyl group 5(8.33%) patients and in the saline group 3(5%) patients had bradycardia being statistically significant.

Table 1: Comparison of demographic parameters

Parameters	Group A	Group D	Group F	P-value
	(n=60)	(n=60)	(n=60)	
Age (years) [mean ± SD]	35.21±9.61	36.89±14.23	37.89±14.68	0.558 (NS)†
Gender [No. (%)]				
Male	41 (68.33)	46 (76.67)	39 (65)	0.569(NS)*
Female	19(31.67)	14 (23.33)	21 (35)	
ASA				
1	57 (95)	55 (91.67)	55 (91.67)	0.669 (NS)*
2	3 (5)	5 (8.33)	5 (8.33)	

Weight (mean ± SD)	64.29±2.69	64.32±1.74	64.98±2.12	0.475(NS)
Height (mean ± SD)	160.12±2.61	160.81±2.84	160.19±3.18	0.587 (NS)
Duration of surgery (mean ±SD)	91.77±16.65	98.26±18.42	99.87±13.36	0.059 (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		Group D		Group F		
	(n=60)	(n=60)	(n=60)	(n=60)	(n=60)	(n=60)	
Onset of sensory block (in min)	10.74	4.11	8.56	2.89	2.18	1.32	< 0.001* (S)
Duration of sensory block (in min)	114.63	7.25	205.17	6.52	162.32	12.84	< 0.001* (S)
Onset of motor block (in min)	11.11	3.87	8.79	3.54	3.45	1.29	< 0.001* (S)
Duration of motor block (in min)	162.04	6.52	254.29	6.72	187.88	11.26	< 0.001* (S)
Time taken to achieve for maximum sensory block (in min)	15.78	4.93	13.36	3.62	5.42	1.87	< 0.001* (S)
Bromage Scale							[No. (%)]
3: Inability to raise leg, flex knee or ankle or move toes	60	100	60	100	60	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=60)	Group D (n=60)	Group F (n=60)	P-value*
T4 dense	0	0	4 (6.67)	< 0.001 (S)
T6 dense	0	8 (13.33)	43 (71.67)	
T8 dense	10 (16.67)	34(56.67)	13 (21.66)	
T10 dense	50 (83.33)	18 (30)	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	28(46.67)
Postoperative recovery	15(25)
0.5hr	17 (28.33)
Group D	
2hr	3(5)
3hr	13 (21.67)
4hr	28 (46.67)
6hr	16 (26.67)
Group F	
Postoperative recovery room	7(11.67)
0.5hr	29(48.33)
1hr	18 (30)
2hr	6 (10)

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

Group/Number of doses in 24 hr.	No. (%)
Group A	
4	21 (35)
5	31 (53.33)
6	8 (13.33)
Group D	
1	4 (6.67)
2	54 (90)
3	2 (3.33)
Group F	
1	5 (8.33)
2	10 (16.67)
3	45 (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 10.74±4.11 min in the saline group and 8.56±2.89 min in the dexmedetomidine group and 2.18±1.32 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 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 Rana [14] 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.*, 2009 [15] 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 15.78±4.93 min, in group D was 13.36±3.62 min and in group F it was 5.42±1.87 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.*, in 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 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. Ghanem M Subhi *et al.*,^[15] (2009) 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 114.63 ± 7.25 min, and in group F was 162.32 ± 12.84 min. and in group D was 205.17 ± 6.52 min. Prolong duration occur in the dexmedetomidine group. Prolong duration occur in the dexmedetomidine group. The prolongation of effect may result from synergism between local anaesthetic and alpha 2 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 11.11 ± 3.87 min, in group D it was 8.79 ± 3.54 min, in group F it was 3.45 ± 1.29 min. Onset of motor block occurred earlier in the fentanyl group. Mohamad Kamal *et al.*, in 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 ± 6.52 min and in group D was 254.29 ± 6.72 min and in group F it was 187.88 ± 11.26 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.* in 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.*, in 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.*, in 2013^[17] and R. Ahmed *et al.* in 2009.^[19] In regard, first analgesic requirement was prolonged in group D as compared to group A and group F and requirement of 24hr 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 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).

Farhad Safari, *et al.*, in 2016^[23] 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 2017^[24] found that the postoperative analgesic requirement in first 24hr 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. 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 pruritus.

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 38 (63.33%) patient in the dexmedetomidine group had bradycardia while in the fentanyl group 5 (8.33%) patients and in the saline group 3 (5%) patients had bradycardia being statistically significant. However there was no episode of bradycardia found in Ahmed Sobhy Basuni *et al.*,^[17] in 2013 and Mohamad Kamal *et al.*, in 2017^[13] studies. Ghanem *et al.*, in 2009^[15] stated that side effect of bradycardia was less because small dose of intrathecal dexmedetomidine was used in their study. In our study, 41 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)^[19] studied they found that 14 (28.0%) patients in group fentanyl and 8 (16.0%) patients in group dexmedetomidine had hypotension.

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.

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