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A COMPARATIVE STUDY OF DEXMEDETOMIDINE AND FENTANYL AS ADJUNCT TO LEVOBUPIVACAINE IN ELECTIVESURGERIES CONDUCTED UNDER SUBARACHNOID BLOCK

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ABSTRACT:

Background and Aim: In modern anaesthesia practice combining small doses of adjuvant like midazolam, clonidine, opioids specially fentanyl to local anesthetics intrathecally improve quality of intraoperative anaesthesia, prolong analgesia and decrease the complications associated with high dose of local anesthetics. Fentanyl provides improved quality of intraoperative and early postoperative subarachnoid block, increased duration of analgesia, but associated with respiratory depression, pruritus and retention of urine. Dexmedetomidine, a highly selective alpha-2 agonist provide stable hemodynamic condition, good quality of intraoperative anaesthesia, prolonged postoperative analgesia, potentiate the action of local anaesthetics with minimal side effects. The present study has been designed to compare the effects of adding dexmedetomidine 5 μgm and fentanyl 25 μgm to 0.5% Levobupivacaine on subarachnoid block characteristics, duration of sensory and motor block, postoperative analgesia and sedation.

Methods: 90 patients of ASA I and II patients of age group 15-50 years posted for elective surgical procedure under spinal anaesthesia were divided into 3 groups of 30 each. Group A (n=30) received 15 mg of Levobupivacaine with 5 μgm dexmedetomidine, Group B (n=30) received 15 mg of Levo bupivacaine with 25 μgm fentanyl and Group C (n=30) received 15 mg of Levobupivacaine with normal saline intrathecally. Duration of surgery, duration of motor block, blood pressure, heart rate (HR) and oxygen saturation ($Sp0_2$) were monitored. Pain assessment was done by Visual Analogue Scale (VAS) till 24 hrs and level of sedation was assessed.

Results: Intraoperative and postoperative sedation score were significantly different among the groups. The haemodynamic response following subarachnoid block was comparable among three groups. Overall side effects like nausea, vomiting, pruritus were significantly different among groups.

Keywords: : Subarachnoid block, VAS score, Sedation, Hemodynamic response.

INTRODUCTION

Spinal anaesthesia is a well-known technique for various infra umbilical surgeries. Compared to Bupivacaine, Levobupivacaine is associated with less vasodilatation, less cardiotoxicity and has longer duration of action. Levobupivacaine is approximately 13 percent less potent (by molarity) than racemic bupivacaine and has longer motor block onset time. Small doses of adjuvants like midazolam, clonidine and opioids like fentanyl are added to Levobupivacaine to improve quality of intraoperative anaesthesia, prolong analgesia and decrease the associatedcomplications.

Fentanyl in various doses (10,20,30,40 μgm) provides improved quality of intraoperative and early postoperative subarachnoid block, increased duration of analgesia, but associated with significant respiratory depression, pruritus and retention of urine.[1,2] Prolongation of duration of analgesia by adding fentanyl with bupivacaine and lignocaine have been demonstrated in obstetric and non-obstetric patients.[3] Intrathecal

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fentanyl exerts its effects by combining with opioid receptors in the dorsal horn of spinal cord and may have a supraspinal spread and action.

Dexmedetomidine, a new highly selective alpha-2 agonist has a variety of actions including potentiating the action of local anaesthetics. Dexmedetomidine was approved primarily by Food and Drug Administration as a short term intravenous sedative agent in mechanically ventilated patients. Dexmedetomidine when used intravenously during anaesthesia reduces opioid and inhalational anaesthetic requirements. It is under evaluation now as a neuroaxial adjuvant. It has been seen to provide stable hemodynamic condition, good quality of intraoperative anaesthesia, prolonged postoperative analgesia with minimal side effects in human studies. Most of the clinical studies about intrathecal alpha-2 adrenoreceptor agonist are related to clonidine. Compared with clonidine, dexmedetomidine is 8 times more specific for alpha-2 adrenoreceptors. Kalso and colleagues reported a 1:10 dose ratio between intrathecal dexmedetomidine and clonidine in animals.[5] Kanazi found that 3 micrograms dexmedetomidine and 30 micrograms clonidine is equipotent intrathecally when added to bupivacaine in patients undergoing urological procedures.[4] Alpha-2 adrenergic agonists prolong sensory block by depressing the release of C-fibre transmitters and by hyperpolarization of postsynaptic dorsal horn neurons.[5] Motor block prolongation may result from binding of these agonists to motor neurons in the dorsal horn of spinal cord.

Considering all these observations, the present prospective double blind randomized study was designed to compare the effects of adding dexmedetomidine 5 μgm and fentanyl 25 μgm to 0.5% Levobupivacaine on subarachnoid block.

MATERIAL AND METHODS:

This double blind randomised study was conducted after obtaining approval from institutional ethical committee. Written informed consents were obtained from all the patients enrolled in the study. Patients of ASA physical status I and II, scheduled for elective surgeries in the Dept of Orthopaedics, O&G and general surgery under subarachnoid block were included in the study. Study variables were Motor and sensory block characteristics, haemodynamic parameters, sedation, adverse effects. Patients having local site infection, spinal deformity, bleeding diathesis, h/o hypersensitivity to the study drugs, cardiovascular (uncontrolled or labile hypertension, heart block, dysrhythmia), renal, metabolic, neurological, and psychiatric disorder, Weight >120 kg were excluded from the study. Sample size of 30 for each of the 3 study groups were assigned with computer generated random numbers getting probability of both type 1 error and type 2 error < 0.05 %.

Group A :Received 15 mg of 0.5% Levobupivacaine in 3 ml and 5 μgm dexmedetomidine in 0.5 ml NS intrathecally.

Group B :Received 15 mg of 0.5 % Levo bupivacaine in 3 ml and 25 μgm fentanyl in 0.5 ml intrathecally.

Group C :Received 15 mg of 0.5 % Levo bupivacaine in 3 ml and 0.5 ml preservative free normal saline intrathecally.

A baseline assessment of all the parameters were taken before administration of spinal anaesthesia. Lumber puncture was performed in sitting position at L3 - L4 intervertebral space through a midline approach using 25 G quincke spinal needle. Sensory block level was tested by loss of pin prick sensation to a 23 G hypodermic needle along the midclavicular line bilaterally every 2 mins until the highest level of sensory block was achieved. Then at every 10 mins until the point of two segment sensory regression from the highest sensory level. In case of abdominal surgeries, sensory regression was checked in posterior axillary line. On achieving T10 sensory block level, surgery was allowed. Time to achieve T10 level of sensory block, highest level of sensory block and time for two segment sensory regression from highest sensory block level were noted.

Motor block level was assessed by modified Bromage scale.[19] Onset of motor block was assessed from injection of local anaesthetic to achievement of motor block of Bromage scale 3. Duration of motor block (in minutes) was measured from the onset of motor block to regaining of full motor power and joint movement (Bromage scale 0). All duration was calculated considering the time of intrathecal injection as zero. Duration of

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surgery was recorded. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and oxygen saturation ($Sp0_2$) were monitored intraoperatively initially at 1 minute interval until 5 minutes, then at 5 minutes interval. Hypotension (SBP < 90 mm of Hg or mean BP < 20% from baseline value) was treated with inj. mephenteramine 6 mg incremental dose as needed. Bradycardia (HR < 60 beats / min) was treated with inj. atropine 0.6 mg intravenously. Oxygen supplementation was given through face mask at the rate of 4-6 litre/minute if $Sp0_2$ became <90%.

In the postoperative period, vital signs like SBP, DBP, HR, $Sp0_2$ were recorded at 15 minutes interval. Pain assessment was done postoperatively by Visual Analogue Scale (VAS) initially every 1 hr for 2 hrs, then every 2 hrs for the next 8 hrs and thereafter every 4 hrs till 24 hrs. Rescue analgesia (inj. diclofenac sodium 1.5 mg / kg i.m.) was given after the numerical pain score being >5. Level of sedation was also assessed by modified Ramsay Sedation Scale[(18)](RSS).

Incidence of adverse effects such as nausea, vomiting, shivering, pruritus, respiratory depression, were recorded by clinical observation, regular conversation with the patient as well as with the surgeon both intraoperatively and postoperatively.

Statistical analysis: Categorical variables were compared among 3 groups by Chi-square test . Scaler parametric data were compared among 3 groups by one way ANOVA followed by Tukey's test or Games Howell's test as post hoc test. Kruskal Wallis H test was done to test significance difference for nonparametric values and ordinal data among three groups, followed by Mann-Whitney U test to test significant difference between two groups. P value < 0.05 was considered statistically significant. All statistical analysis was done using SPSS 16.0 version.

OBSERVATION AND RESULTS:

Table 1 - Distribution of age (in years),body weight(in kilograms),height in cm and duration of operation in minutes in the three groups.

	Group A	Group B	Group C	p-value		
	Mean±SD	Mean±SD	Mean±SD	Gr A & Gr B	Gr B & Gr C	Gr C &Gr A
Age	44.06±5.29	43.6±6.60	43.53±5.87	0.950	0.299	0.936
Weight	48.8±3.65	48.73±3.52	47.3±5.04	0.997	0.415	0.391
Height	160.20±3.03	160.10±3.25	160±2.86	0.991	0.991	0.965
Duration	98.36±8.69	98.86±8.44	97.7±7.98	0.971	0.852	0.949

Statistical analysis shows p-value>0.05 for each 2 groups. So, the groups were comparable.

Table 2- Distribution of patients in groups according to ASA-Physical Status

	ASA-PS I	ASA-PS II
Group A	23(76.7%)	7(23.3%)
Group B	24(80%)	6(20%)
Group C	22(73.3%)	8(26.7%)

P=0.830.the three groups were comparable regarding ASA-PS of their patients.

Table 3– Comparison of subarachnoid block characteristics among the three groups

Level of block in minutes	Group A	Group B	Group C	p-value		
	Mean±SD	Mean±SD	Mean±SD	Gr A&Gr B	Gr B&Gr C	Gr C&Gr A
Time to reach T10 sensory block level	5.3±0.59	6.03±0.41	6.73±0.44	0.000	0.000	0.000
Highest level of sensory block	T4/T5/T6 19/8/3	T4/T5/T6 17/11/2	T4/T5/T6 3/8/19			
Time to reach highest level of sensory block	7.53±0.59	9.46±0.73	13.06±1.25	0.000	0.000	0.000
Time to reach	7.93±0.60	9.13±0.94	11.4±0.65	0.000	0.000	0.000

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Bromage-3 motor block						
Time for two segment sensory regression	107.16±3.15	95±5.00	82.83±3.15	0.000	0.000	0.000
Regression time to reach Bromage-0	206.33±3.09	189.66±4.95	155.66±3.12	0.000	0.000	0.000

Table 4- Comparison of intra operative sedation

	Group A	Group B	Group C	p-value		
	1/2/3	1/2/3	1/2/3	Gr A and Gr B	Gr B and Gr C	Gr C and Gr A
At 30 minute	0/9/21 (0%/30%/70%)	1/20/9 (3.3%/80%/16.7%)	2/28/0 (6.7%/100%/6.7%)	0.000	0.001	0.000
At 60 minute	0/6/24 (0%/20%/80%)	0/18/12 (0%/83.3%/16.7%)	0/30/0 (0%/100%/0%)	0.000	0.001	0.000
At 90 minute	0/6/24 (0%/20%/80%)	0/18/12 (0%/83.3%/16.7%)	0/30/0 (0%/100%/0%)	0.000	0.001	0.000

Table 5 - Comparison of postoperative sedation

	Group A	Group B	Group C	p-value		
	2/3	2/3	2/3	Gr A and Gr B	Gr B and Gr C	Gr C and Gr A
At 2 hour	6/24 20%/80%	25/5 83.3%/16.7%	30/0 100%/0%	0.000	0.000	0.000
At 4 hour	12/18 40%/60%	24/6 80%/20%	30/0 100%/0%	0.002	0.000	0.000
At 8 hour	17/13 56.7%/43.3%	27/3 90%/10%	30/0 100%/0%	0.004	0.002	0.004
At 16 hour	18/12 60%/40%	27/3 90%/10%	30/0 100%/0%	0.008	0.002	0.002
At 24 hour	20/10 66.7%/33.3%	28/2 93.3%/6.7%	30/0 100%/0%	0.010	0.001	0.001

Patients of group A had significantly higher level of sedation in the post operative hours compared to patients of group B and C. Patients of group C were awake and irritable.

Table 6 - Comparison of pain score in the first post operative hour

	Group A	Group B	Group C	p-value		
VAS score	0/1/2/3/4	0/1/2/3/4	0/1/2/3/4	Gr A & Gr B	Gr B & Gr C	Gr C & Gr A
1st hour	28/2/0/0/0 (93.3%/6.7%/0%/0%/0%)	0/5/21/4/0 (0%/16.7%/70%/13.3%0%)	0/0/2/6/22 (0%/0%/6.7%/20%/73.3%)	0.000	0.000	0.000

Table 7 -Comparison of pain score in subsequent post operative hours(upto 24 hrs)

	Group A	Group B	Group C	p-value		
VAS score	0/1/2	0/1/2	0/1/2	Gr A and Gr B	Gr B and Gr C	Gr C and Gr A

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At 4 hour	12/13/5 (40%/43.3%/16.7%)	12/15/3 (40%/50%/10%)	13/13/4 (43.3%43.3/0%/13.3%)	0.771	0.942	0.729
At 8 hour	11/17/2 (36.7%/56.7%/6.7%)	10/15/5 33.3%/50%/16.7%	7/14/9 23.3%/46.7%/30%	0.483	0.214	0.067
At 12 hour	11/17/2 (36.7%/56.7%/6.7%)	7/16/7 23.3%/53.3%/23.3%	9/17/4 30%/56.7%/13.3%	0.088	0.345	0.431
At 16 hour	12/15/3 40%/50%/10%	10/16/4 33.3%/53.3%/13.3%	10/16/4 33.3%/53.3%/13.3%	0.555	1.000	0.555
At 20 hour	7/17/6 23.3%/56.7%/20%	9/16/5 30%/53.3%/16.7%	10/14/6 33.3%/46.7%/20%	0.559	0.974	0.559

Table 8-comparison of time for rescue analgesia

	Group A	Group B	Group C	p-value		
	Mean±SD	Mean±SD	Mean±SD	Gr A and Gr B	Gr B and Gr C	Gr C and Gr A
Duration of analgesia	290.66±6.11	210.66±9.94	142±6.18	0.000	0.000	0.000

Table 9-Incidence of side effects among study groups

Side effects	Group A	Group B	Group C
Bradycardia	1	0	0
Hypotension	3	2	0
Nausea/Vomiting	1	3	1
Pruritus	0	2	0
Urinary retention	0	0	0

DISCUSSION

Infraumbilical surgeries are often done under spinal anaesthesia with 0.5 % hyperbaric bupivacaine being traditionally used. Compared to Bupivacaine Levobupivacaine is associated with less vasodilation, less cardiotoxic, longer duration of action. Rita Compagna, Gabriele Vigliotti[(6)] in 2012 concluded that clinical efficacy of Levobupivacaine and racemic bupivacaine were equally effective in hernioplasty surgery, Levobupivacaine could be preferred.

But the anaesthesia provided by Levobupivacaine alone may be too short for the planned surgery. Local anaesthetics with opioids demonstrate significant synergy. They provide excellent analgesia with lower drug requirements. This results in rapid onset, limited and brief spread. Intrathecal fentanyl produces selective spinal analgesia which offers better haemodynamic stability and allows early ambulation. The prolongation of the duration of spinal analgesia produced by intrathecal fentanyl is not dose related.

Singh H and co-workers[(7)] investigated the effect of intrathecal fentanyl (25 μg) on the onset and duration of bupivacaine (13.5 mg) on urological procedures, and found that addition of fentanyl prolonged the duration of sensory block and reduced the analgesic requirement in the early postoperative period. Seewal R and colleagues[(8)] studied the effect of adding various doses of fentanyl to intrathecal 0.5% hyperbaric bupivacaine on perioperative analgesia and subarachnoid block characteristics in lower abdominal surgeries and concluded that fentanyl in various doses (10,20,30,40 μgms) significantly reduced somatic and visceral pain and prolonged the time of regression of sensory block. The author found no further increase in the duration of analgesia when the dose of fentanyl was increased from 10 μg to 20, 30, or 40 μg**.** Varrasi G et al[(9)] observed ventillatory effects of subarachnoid fentanyl in elderly patients. They recommended 25μg fentanyl as the only intrathecal dose which gives significant analgesia without respiratory depression in elderly patients.

Dexmedetomidine is a highly selective alpha-2 adrenoreceptor agonist approved as intravenous sedative drug. It is not a result of altered systemic absorption, as the plasma level of bupivacaine was not altered after the addition of intrathecal clonidine to bupivacaine . It may be an additive or synergistic effect

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secondary to their different mechanism of action. T.Yaksh TL[10] has shown that intrathecal α2-adrenoceptor agonists can cause a dose-dependent decrease in motor strength in animals. The prolongation of the motor block of spinal anaesthetics may result from the binding of α-2 adrenoceptor agonists to motor neurons in the dorsal horn. Clinical studies in surgical patients showed that intrathecal clonidine increases the duration of sensory and motor block, this effect of clonidine is dose-dependent. Moreover**,** KaLso E and colleagues[11] reported a 1: 10 dose ratio between intrathecal dexmedetomidine and clonidine in animals**.** Al-Mustafa MM and co-workers[12] conducted a study to determine the effect of adding dexmedetomidine (5 μgm and 10 μgm) to spinal bupivacaine (12.5 mg) in urological surgeries and concluded that dexmedetomidine prolongs the duration of sensory and motor block significantly in a dose dependent manner**.** Al-Ghamenet al.[13] showed more prolonged motor and sensory block and less side effects with intrathecal 5 μgm dexmedetomidine, compared to 25 μgm fentanyl, combined with 10 mg isobaric bupivacaine. Rajni Gupta[14] and co-workers demonstrated more prolonged motor and sensory block and reduced demand for rescue analgesics in 24 hour period with 5 μgm dexmedetomodine, compared to 25 μgm fentanyl, combined with 12.5 mg hyperbaric bupivacaine in lower abdominal surgeries.

In the present study, there was significantly early onset of sensory block in group A (dexmedetomidine group). The time to achieve T10 level of sensory block was significantly early in group A compared to both group B (fentanyl group) and group C (control group). (Group A=5.3 ± 0.59min, Group B -6.03 ± 0.41 min, p <0.0001)(Group A=5.3 ± 0.59 min, Group C = 6.73 ± 0.41 min, p < 0.0001).

The highest levels of sensory block were comparable in Group A and Group B. But the time to achieve the highest sensory block level was significantly early in group A compared to both group B and group C. (Group A = 7.53 ± 0.59 min, Group B = 9.46 ± 0.73 min, p < 0.0001) (Group A = 7.53 ± 0.59 min, Group C = 13.06 ± 1.25 min, p < 0.0001).

The time to achieve Bromage 3 level of motor block were (Group A = 7.93± 0.60 min, Group B = 9.13 ± 0.94 min, p <0.0001; (Group A = 7.93 ± 0.60 min, Group C = 11.4 ± 0.65 min, p < 0.0001).

Two segment sensory regression time (from highest sensory block level) was significantly longer in group A compared to group B and control group (Group A = 107.16 ± 3.15 min ,Group B = 95 ± 5 min, p < 0.0001; Group A = 107.16± 3.15 min, Group C = 82.83 ± 3.15 min, p < 0.0001) and also in group B compared to control group (Group B = 95±5 min, Group C = 82.83 ± 3.15 min, p < 0.0001). Similar findings were also observed in mean regression time of motor block to reach Bromage 0 (Group A = 206.33 ±3.09 min, Group B = 189.66 ±4.95 min, p <0.0001 ; Group A = 206.33 ± 3.09 min, Group C = 155.66 ± 3.12 min, p < 0.0001 ; Group B = 189.66 ± 4.95 min, Group C = 155.66 ± 3.12 min, p < 0.0001). Similar finding was also observed by Tiwari J P, Tripathi D K[15]. They added 5μg Dexmedetomidine to 3 ml of Isobaric Levobupivacaine with 0.5 ml of Normal saline with 3 ml of Levobupivacaine in gynaecological surgeries. They found that two segment sensory regression, S2 segment regression and the regression of motor block to Bromage 0 were significantly slower with dexmedetomidine as compared to intrathecal fentanyl. .

In both studies Dexmedetomidine group achieves early onset of T 10 block, Bromage 3 motor block, highest level of sensory block and late onset of 2 segment regression, Bromage 0 level compared to Normal saline (control) group. Similar comparison also observed in Fentanyl with Normal saline (control) group.All the differences are statistically significant. Patients of group A in our study had significantly higher level of sedation (RSS 3) compared to group B (RSS 2) (p < 0.0001) and group C (RSS 2) (p < 0.0001), in both intra and postoperative period.

In our study, all the patients in the three groups maintained good haemodynamic stability and oxygen saturation both in intraoperative and postoperative period. Only three patients in group A and two patients in group B developed mild hypotension in the intraoperative period. One patient in group A had bradycardia (heart rate < 60 beats / min). The most significant side-effects reported about the use of intrathecal α2 adrenoreceptor agonists are bradycardia and hypotension. In the present study, these side effects were not significant probably because we used small dose of intrathecal dexmedetomidine which was also confirmed by Kanazi GE in his study.[16]

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Oxygen supplementation through face mask was needed for only two patients in group B who desaturated intraoperatively ($Sp0_2$< 90% for 10 seconds**).** Gupta R et al [(14)] and in our study, no patient required intraoperative analgesic. In the first postoperative hour 73.3% of group C had VAS score > 3. But all the patients of group A and group B had VAS score < 3 and the difference is statistically significant (p < 0.0001).

The mean time to demand rescue analgesics was 290.66 ± 6.11 minutes in group A, which was significantly longer compared to both group B (210.66 ± 9.94 minutes) (p < 0.0001) and group C (142± 6.18 minutes)(p < 0.0001). Time taken by group B patients to demand rescue analgesics was also significantly prolonged than the control group (p<0.0001). Tiwari J P ,Tripathi D K[(15)] , and Joginder pal Attri ,Gagandeep kaur[(17)] observed significantly longer duration of postspinal analgesia in dexmedetomidine group compared to fentanyl group using isobaric Levobupivacaine. VAS scores were comparable among the three groups in the first twenty-four postoperative hours.

Two patients of group B complained of pruritus. Pruritus after intrathecal fentanyl is reported to be 40-70% but it was only 13% in the present study which can be explained by the fact that pruritus is a benign subjective symptom which is underreported and usually need no treatment. Three patients in group B and one patient in each group A and group B complained of nausea, vomiting in the postoperative period. No patient developed hypotension, bradycardia, respiratory depression, urinary retention in post operative care unit.

CONCLUSION:

Dexmedetomidine (5 μgms) seems to be a better alternative to fentanyl (25 μgms) as additive to intrathecal isobaric Levobupivacaine (12.5 mg) since it produces more prolonged sensory and motor block with similar kind of haemodynamic stability, better postoperative analgesia and sedation and is associated with less adverse effects. This kind of block may be more suitable for infraumbilical surgeries of longer duration. Intrathecal dose of dexmedetomidine used in the present study needs further clinical studies to prove its efficacy and safety and to be considered as the suitable dose of dexmedetomidine for supplementation of spinal local anaesthetics.

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