Original Research Paper

Volume-8 | Issue-7 | July-2018 | PRINT ISSN No 2249-555X

Anesthesiology

COMPARISON OF THREE DIFFERENT DOSES OF DEXMEDETOMIDINE IN SUBARACHNOID BLOCK AS AN ADJUNCT TO BUPIVACAINE IN LOWER LIMB ORTHOPAEDIC SURGERY.

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ABSTRACT Dexmedetomidine is used to prolong the spinal subarachnoid block quiet often. However, the range of its dose is wide and varies from 3 mcg to 15 mcg. We compared three different doses of Dexmedetomidine to find out the optimum dose at which adequate prolongation of analgesia can be achieved without any adverse effect. **Method:** 120 ASA grade 1 patients of proposed lower limb orthopedic surgery were divided into four groups using randomization chart. All groups received 3.2ml 0.5% heavy bupivacaine for spinal SAB. For group D1: Dexmedetomidine 5µg, for group D2: Dexmedetomidine 10µg, for group D3: Dexmedetomidine 15 µg and for group B (control): 0.3 ml normal saline was added to Bupivacaine. **Results:** Onset of sensory blockade was significantly early in group D3 (mean 4.33±0.758) than D1 (mean 8.33±0.758) and control group (9.33±0.959) minutes. Motor block followed similar trend. Two segment regression of block was also significantly late in group D3 (mean 173.5± S.D. 12.875) compared to D2 (154±8.749min), D1 (137.5±5.686) and B (89.5±10.776) minutes. Mean total duration of analgesia in group D3 (313.17±21.515 min) was also significantly higher compared to D2 (276±10.86 min) and D1 (241.83±15.563 min) and control (188±8.57 min) groups. No significant differences were found in hemodynamic and respiratory parameters amongst all four groups. Incidence of adverse events was also comparable in all four groups. **Conclusion:** Dexmedetomidine prolongs the duration of sensory and motor block and overall duration of analgesia in dose dependant manner. 15 µg Dexmedetomidine, the maximum dose used in our study has stable hemodynamic and respiratory profile.

KEYWORDS : Dexmedetomidine, spinal, analgesia, hemodynamics.

Introduction:

Effective management of perioperative pain after orthopedic surgery is an important component of early postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential of decreasing perioperative morbidity [1].

For decades, spinal subarachnoid block [SAB] has remained one of the most popular, reliable, and safe techniques that can provide anaesthesia and analgesia for a variety of lower limb orthopedic surgeries. [1, 2] It exerts anesthetic and analgesic effect by inhibiting nociceptive transmission from peripheral to central neuronal system One of the main disadvantages of subarachnoid block anaesthesia is the short duration of action. Many times, it demands supplementation of extra dose of analgesics through a preplaced epidural catheter or conversion to general anaesthesia in prolonged procedures. [3,4]. Short duration also leads to early waning of analgesia in postoperative period which demands early introduction and sometimes combination of other routes of analgesia in postoperative period. This in turn creates need for techniques to prolong this efficient mode of analgesia.

Prolongation of subarachnoid block has been achieved by the addition of various adjuvants, such as Opioids [5], Epinephrine , Neostigmine, Magnesium [6],Midazolam, Ketamine [7] and Clonidine[8,9] Dexmedetomidine is a newer α2 adrenergic agonist having 8 times higher selectivity for α 2A receptors than Clonidine, responsible for the hypnotic and analgesic effects of these drugs. [10, 11]. A There is a large body of recent evidences supporting favourable profile of Dexmedetomidine in spinal anaesthesia [12,13, 14]. However, there is a wide variation in the doses of Dexmedetomidine used in these studies ranging from 3 µg to 15 µg. It is evident that duration of analgesia increases with addition of Dexmedetomidine in dose dependant manner but this is coupled by increase in side effects too [15,16]. Studies to find optimum dose of Dexmedetomidine at which there will be maximum prolongation of analgesia can be achieved without significant increase in adverse effects are still lacking.

We performed this prospective, randomized double- blinded study to evaluate the analgesic efficacy and adverse effects of three different doses of Dexmedetomidine with Bupivacaine in subarachnoid block for lower limb orthopaedic surgeries.

Methods:

Institutional ethical committee approval was obtained. 120 adults of either sex belonging to ASA class I posted for lower limb surgery under subarachnoid block, were enrolled for this study. All the patients were between the ages of 18 and 60. Patients with history of hypertension, cardiovascular, liver diseases and convulsions were excluded from study. Also, patients using adrenergic receptor blockers calcium channel blocker were excluded. Written informed consent was obtained from all the patients. Using randomisation chart, patients were assigned to one of the four groups depending on the study drug they would receive:

Group B: 0.5% heavy Bupivacaine 3.2 ml (15mg) plus normal saline.

Group D1: 0.5% heavy Bupivacaine 3.2 ml (15mg) and Dexmedetomidine 5µg.

Group D2: 0.5% heavy Bupivacaine 3.2 ml (15mg) and Dexmedetomidine 10µg.

Group D3: 0.5% heavy Bupivacaine 3.2 ml (15mg) and Dexmedetomidine 15 µg. Volume of study drug was made 0.3 ml in all cases to make final volume of injectate 3.5 ml for blinding purpose.

In the operating theatre, patient was connected to and monitored using electrocardiograph (ECG) monitor, a pulse oximeter, non-invasive blood pressure (NIBP) monitor. 350 ml Intravenous Ringer's lactate was administered through an 18 G IV cannula over 15 mins to each patient as to cover the fasting deficit. Spinal subarachnoid block was performed after this at the L2-3 or L3-4 vertebral level using 25-gauge-Quinkey's needle by midline approach with patients in the sitting position. Rate of injection will be kept constant 0.2 ml/sec using a stop watch. Patients was made supine following the block immediately.

The anaesthesiologist who performed the block and record the parameters was blind regarding the study group to which patient belongs. The onset (defined as absence of pain at the T8 dermatome) and duration of sensory block (regression of block height to L1) , highest level of sensory block, time to reach the highest dermatomal level of sensory block, motor block onset, time to complete recovery of motor block, and duration of spinal anaesthesia was recorded. The motor level was as per Bromage score[17].

Vital parameters like Heart rate, Systolic BP, Diastolic BP, Mean BP, Respiratory Rate, SPO2 was recorded at 5 min before intrathecal injection; 5, 10, 15, 20, 25 and 30minutes after intrathecal injection, subsequently every 15 minutes till completion of surgery. Pain scores

using verbal pain scale was recorded 5 min before intrathecal injection, after the start of surgery, and subsequently every 30 min till the surgery is over and degree of pain was assessed every 1 hour thereafter.

Results:

The three groups were similar in terms of age, weight, sex, ASA physical status and duration ofsurgery ($p > 0.05$). The baseline haemodynamic parameters in all three groups were comparable and not statistically significant ($p > 0.05$).

The highest sensory level achieved: number of patients having highest level of sensory block was comparable in all the groups. The highest level in all the study group was T6.

Table 1: Highest level of spinal Block in each group

	Groups				P value
Max spinal level	B	D1	D2	D3	
T6	20(66.70 %)	25(83.30%)	26(86.66%)	25(83.30%)	0.285
T8	10(33.30 %)	5(16.70%)	4(13.33%)	5(16.70%)	

Mean duration of surgery in group D3 were 171 ±12.205 ,in group D2 172± 12.29 ,in group D1 171.5± 10.184 , in group C 171±10.12 . (no significant difference, $P > 0.05$ by Annova)

Comparison of Characteristics of Sensory and Motor blocks between study groups:

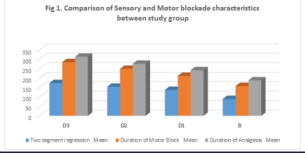
Table 2 shows that the onset of sensory blockade was faster in Group D3 (4.33 ± 0.758 min.) as compared to Group D2 (6.27 ± 0.691 min.) Group D1 (8.33± 0.758) and Group B (9.33± 0.959). Also, onset of motor blockade was faster in Group D3 (7.13 ± 1.008 min.) as compared to Group D2 (8.47± 0.86 min.) Group D1 (9.33± 0.959) and Group B (9.73± 0.691). ($P < 0.05$).

Table 2: Comparison of Sensory and Motor blocks between study group

Parameters	Groups				P value
	D3	D2	D1	B	
Onset of Sensory block Mean(±SD)	4.33±0.758	6.27±0.691	8.33±0.758	9.33±0.959	<0.01
Onset of Motor Block Mean (±SD)	7.13±1.008	8.47±0.86	9.33±0.959	9.73±0.691	< 0.01
Two segment regression Mean (±SD)	173.5±12.875	154±8.749	137.5±5.686	89.5±10.776	<0.01
Duration of Motor Block Mean (±SD)	284.5±13.918	249±10.12	211.67±14.759	158±8.57	<0.01
Duration of Analgesia Mean (±SD)	313.17±21.515	276±10.86	241.83±15.563	188±8.57	< 0.01

ANOVA NS: Not significant

Time required for two segment regression of sensory block is significantly prolonged in Group D3 (173.5 ±12.875 min.) as compared to Group D2 (154 ± 8.749 min.) Group D1 (137.5±5.686) and Group B (89.5±10.776). Group D2 has more 2 segment regression time than Group D1 and Group B. Group D1 shows prolonged 2 segment regression time than Group B. Statistically significant difference was found by applying ANOVA test. ($P < 0.05$). (fig 1)



Similarly, duration of motor block was significantly prolonged in Group D3 (284.5 ±13.918 min.) as compared to Group D2 (249 ± 10.12 min.) Group D1 (211.67±14.759) and Group B (158±8.57) .

Also, dose dependant prolongation of duration of analgesia was seen in Group D3 (313.17 ± 21.51 min) as compared to Group D2 (276 ± 10.86min) Group D1 (241.83± 15.563) and Group B (188± 8.57). This difference was statistically significant (ANOVA test: $P < 0.05$).

Haemodynamic parameters:

Comparison of heart rate between Group D3, Group D2, Group D1 and group B:

The Baseline mean heart rate was 91.3± 6.634 bpm in group D3 ,93.03± 5.738 per min in group D2 ,92.27± 6.319 in group D1 and 91.37± 6.43 bpm in group C and this difference was statistically not significant. ($p > 0.05$) [table 3]

Table 3: Comparison of heart rate in all four groups:

Heart Rate (per Min)	Group D3		Group D2		Group D1		Group B		P Value
	Mean	Sd	Mean	Sd	Mean	Sd	Mean	Sd	
Preinduction	89.33	6.687	90.33	5.738	89.87	7.026	89.8	6.567	0.949*
Induction	91.3	6.634	93.03	5.738	92.27	6.319	91.73	6.438	0.737*
4min	87.08	6.615	89.63	5.229	87.9	5.803	88.67	5.903	0.604*
10 Min	84.2	5.416	86.3	4.466	85.07	5.139	86.03	5.461	0.375*
15 Min	82.07	5.212	83.73	4.127	82.77	4.194	84.2	4.529	0.310*
20 Min	79.17	5.025	80.07	3.732	80	4.698	82.2	3.692	0.049
25 MIN	76.4	4.938	77.13	3.137	77.03	4.303	80.37	3.774	0.001
30 MIN	72.93	4.777	75.47	2.46	75.57	3.892	78.87	3.963	<0.01
45 MIN	71.03	4.817	73.07	2.273	74.77	3.52	76.87	4.321	<0.01
60 MIN	69.7	4.308	71.2	2.441	73.67	3.565	76.07	3.453	<0.01
90 MIN	67.67	4.365	69.2	2.657	72.57	3.213	77.1	3.754	<0.01
120 MIN	69.03	4.106	70	2.678	73.7	3.271	78.07	3.695	<0.01
150 MIN	69.0	4.137	71.27	2.132	74.77	3.319	79.4	4.073	<0.01
POST OP	72.27	3.886	73.07	2.612	76.2	2.987	84.33	4.428	<0.01

ANOVA TEST ***- significant**

At 15 mins after spinal blockade a decrease in heart rate between all four groups by ANOVA test as $P < 0.05$, but this fall in heart rate was statistically significant in D1, D2 and D3 groups. This fall in heart rate continued further but it never went below the physiological limits. Maximum drop n heart rate was seen in group D3 between 90 to 150 mins after induction. The lowest heart rate in D3 was 67.67+ 4.365 at 90 mins while it was 69.2 ± 2.657 bpm at in D2 and 72.57 ± 3.213 bpm at 90th min in D1. 72.57 ± 3.213 bpm at 90th min. Heart rate showed least variation in control group. [fig. 2]

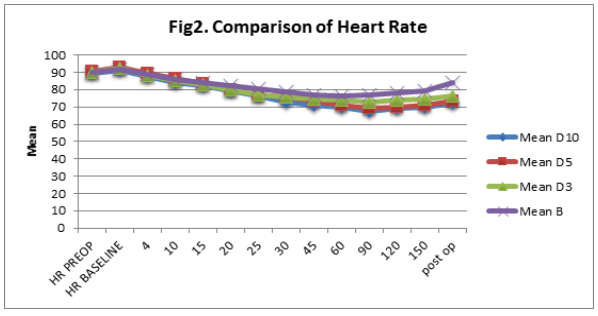
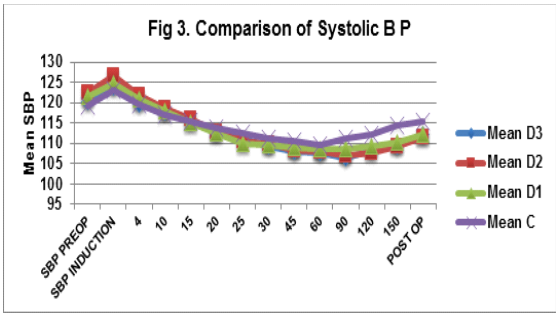


Table 4. Changes in Systolic blood pressure (SBP)

SBP (Mmhg)	Group D3		Group D2		Group D1		Group B		P Value
	Mean	Sd	Mean	Sd	Mean	Sd	Mean	Sd	
Preinduction	120.2	6.687	122.6	5.738	121.4	7.026	119.33	6.567	0.361*
Induction	123.9	5.756	126.57	7.903	124.67	5.467	123.13	5.865	0.187*
4min	119.6	5.184	121.73	6.405	120.87	4.776	119.6	5.152	0.347*
10 Min	117.63	3.662	118.67	5.365	117.93	4.185	117	4.541	0.545*

15 Min	115.37	3.828	116.07	4.472	115.97	4.001	115.33	4.147	0.839*
20 Min	112.73	3.463	112.8	3.916	112.4	3.578	113.9	4.221	0.454*
25 Min	111.1	2.975	110.63	3.045	110	3.063	112.4	3.5	0.029*
30 Min	109.13	2.813	110.03	2.526	109.67	2.523	111.07	3.311	0.061*
45 Min	107.87	2.569	108.27	2.392	108.87	2.27	110.67	2.695	<0.01
60 Min	107.6	2.43	108	7.464	108.67	2.187	109.6	2.372	0.008*
90 Min	106.4	2.253	107	3.184	108.53	2.345	111.7	2.408	<0.01
120 Min	108.87	2.662	107.73	3.14	109.27	2.132	112.27	2.716	<0.01
150 Min	109.93	2.713	109.93	3.003	110.2	2.483	114.27	2.73	<0.01
Post Op	112.13	2.776	111.67	2.631	112.27	2.612	115.27	3.581	<0.01

As seen in Table 4, the baseline mean BP in group D3 was 123.9±5.756 mm Hg. There was a slow and gradual decline in SBP over period after induction with nadir near 90 mins (106.4±2.253 mmHg). Baseline mean BP in group D 2 was 126.57±7.93 mmHg and in group D 1 was (124.67±5.467) mmHg and were comparable to D3. While lowest SBP in group D2 and D1 was (107±3.54 mmHg) and (124.67±5.467) mmHg respectively. Although this drop in SBP was statistically significant, it was not significant clinically as it was well within physiological range. Group C also had some decreases in SBP but it was less siginificant. The maximum drop in SBP in group C was 10.99% while it was 15.459% and 14.188% in D3 and D2 respectively. [fig 3]

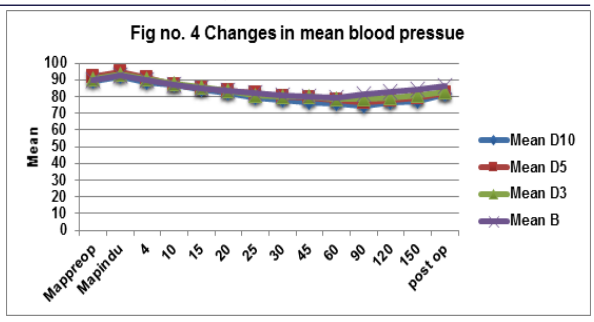


Diastolic and mean blood pressure followed trends similar to that of SBP: The Baseline Mean blood pressure was (92.07+ 4.698) mmHg in group D3, (94.46+5.094) mmHg in group D2 , (93.33 +4.165) in group D1 and (92.67+ 5.029) mmHg in group B. This difference was statistically not significant (p > 0.05).

Table 5. Changes in mean blood pressure(MBP):

MAP (mmHg)	Group D3		Group D2		Group D1		Group B		P Value
	Mean	Sd	Mean	Sd	Mean	Sd	Mean	Sd	
Preinduction	89.22	5.859	91.68	8.835	90.49	4.939	89.8	5.77	0.504*
Induction	92.07	4.698	94.46	5.094	93.33	4.165	92.67	5.029	0.235*
4min	88.76	4.003	90.93	4.186	90.29	3.582	89.69	4.305	0.197*
10 Min	86.72	2.906	87.37	7.982	87.87	3.392	87.24	3.692	0.845*
15 Min	84.54	2.922	84.62	8.117	85.5	3.135	85.24	3.189	0.843*
20 Min	82.29	2.541	83.42	3.314	83.2	2.686	83.52	3.085	0.35*
25 Min	79.54	3.565	82.03	7.869	80.76	2.811	82.22	2.814	0.109*
30 Min	77.89	2.638	80.29	5.524	80.18	2.476	81.02	2.695	0.006*
45 Min	76.67	2.494	79.52	7.306	79.64	1.859	80.08	2.342	0.007*
60 Min	75.93	2.147	77.92	6.236	78.62	2.108	79.3	2.034	0.003
90 MIN	74.4	1.946	76.18	2.248	78.32	6.562	81.3	2.205	0.001
120 Min	76.29	2.212	77.56	2.175	79.53	6.795	82.53	2.245	0.002
150 Min	77.13	2.297	79.09	2.141	80.64	7.228	84.09	2.308	0.001

As per table no. 5, decrease in Mean blood pressure between all four groups were statistically not significant from induction till 25 mins by ANOVA test as P > 0.05. Thereafter MAP dropped by 14.122 + 3.671 at 30 mins and by 17.611 + 4.511 4.511 at 90 min. Maximum decrease in blood pressure in D2 was 18.278+ 4.99, 15.011+ 6.11 in D1 and 11.644+ 4.053 mmHg in group C. However this drop in MAP persisted for a smaller time in group C. [fig 4]



Respiratory profile:

The mean Respiratory Rate was statistically comparable at all the respective intervals between group D3, group D2, group D1 and group B. (p >0.05). Also, The mean Spo2 was statistically comparable at all the respective intervals between all four groups . (p >0.05). None of the patients in all four groups had apnea or saturation SPO2 below 98%.

Adverse Events: 2 patients (6.70%) in group D3 and 1 (3.30 %) patient in Group D2 showed bradycardia. No patient in group D1 and Group C showed bradycardia. Incidence of bradycardia in this study was statistically not significant. (P =0.288). 2 (6.70 %) patients each in Group D3 and Group D2 showed hypotension and 1 (3.30 %) patient in Group D1 and Group B showed hypotension. Incidence of hypotension in our study is statistically not important.(P =8.837). 2 (6.70%) patients in Group D3, 1(3.30%) patients in Group D2, 1(3.30%) patients in group D1 and 1(3.30%) patients in group C shows postoperative nausea and vomiting. (P value 0.89: Chi Square test)

Discussion:

Regional anaesthesia for lower extremity has been extensively studied in literature. Central neuraxial anaesthesia provides excellent anaesthesia, decreases the incidence of deep venous thrombosis and pulmonary embolism and postoperative lung complications in patient who require surgical stabilization[1, 2, 18]. One of the main disadvantages of subarachnoid block anaesthesia is the short duration of action. In this prospective, randomised double blinded study on traumatised lower limb orthopaedic surgeries we have compared the effect of adding 15 µg , 10 µg and 5 µg of Dexmedetomidine added to 3.4 ml of 5 % hyperbaric Bupivacaine on haemodynamic and respiratory profile, analgesic efficacy, on onset time and duration of sensory and motor block as well as adverse effect if any.

It is seen from the statistics that the demographic profile and baseline hemodynamic and respiratory variables were comparable in all the groups. The maximum height of sensory block was similar, T 6-8 in study group and shows no statistically significant difference.

The onset of sensory block, defined as the time taken for sensory block at T8 dermatome, was faster in Group D3 (4.33 ± 0.758 min.) as compared to Group D2 (6.27 ± 0.691 min.) Group D1 (8.33±0.758) and Group B (9.33±0.959). similarly, onset of motor block was also faster in Group D3 (7.13 ± 1.008 min.) as compared to Group D2 (8.47 ± 0.86 min.) Group D1 (9.33±0.959) and Group B (9.73±0.691). Al Mustafa et al[16] also found that Dexmedetomidine produced earlier onset of sensory block in dose dependent manner. The mean time for onset of sensory block was 4.7 +/-2.0 minutes in D10 group. Anjan Das et al [19] also found that median time taken to achieve T10 level sensory block was earlier in the D3 group than the D2 group (4.6 min and 4.8 min, respectively). Similarly, time for maximum motor block was also less in the D3 group than the D2 group (5.46 min and 5.54 min, respectively) in their study. No specific explanation of this phenomenon could be obtained. But increase in no. of molecules capable of producing analgesia by binding to the spinal receptors may be responsible for early onset of blockade. This again points to the inherent local analgesic property of Dexmedetomidine. Kim JE et al [20] also had similar findings of early onset sensory as well as motor blockade in Dexmedetomidine than saline group (p<0.01). In our study duration of motor blockade i.e. time for two segment regression of sensory showed statistically significant and dose dependent prolongation. Duration of sensory block in Group D3 (173.5 ±12.875 min) was more as compared to Group D2 (154 ± 8.749 min) Group D1 (137.5±5.686) and Group B (89.5±10.776). Similar phenomenon of dose dependent prolongation was also seen with motor block duration with zenith in Group D3 (284.5 ±13.918 min) and nadir in Group B (158±8.57). Possible mechanism of action of intrathecal α 2 adrenergic

agonists may be their additive or synergistic effect of local anaesthetics. The local anaesthetics acts by blocking sodium channels, whereas α 2 agonists acts by binding to presynaptic C fibres and post synaptic dorsal horn neurons. Intrathecal α 2 adrenergic agonists produces analgesia by depressing the release of C – fibre transmitters and by hyperpolarization of post synaptic dorsal horn neurons.

Susanta Haldar et al[21] , found that two segment sensory regression time were significantly ($p<0.05$) delayed in D10 group when compared with D5 group (160.63 vs. 130.12 mins) which means increased Dexmedetomidine at subarachnoid space had produced more sustained sensory block. Motor block regression to modified Bromage 0 were also significantly ($p<0.05$) prolonged in group D10 than D5 (164.08 vs 128 min respectively).

In our study duration of analgesia in postoperative period was assessed by Verbal pain scale. Any patient showing pain score more than or equal to 3 will be administered a rescue dose of Inj. Tramadol. Dose dependant prolongation of duration of analgesia in Group D3 (313.17 ±21.51 min) as compared to Group D2 (276 ±10.86 min.) Group D1 (241.83±15.563) and Group C (188±8.57). Anjan Das et al [19] also had it 366.6 min and 242.1 min in the D10 and D5 group respectively.

Haemodynamic parameters:

Heart rate remained near normal in all four groups till 15 mins after SAB. Thereafter all four groups showed statistically significant decrease in ($P > 0.05$).

But this fall in heart rate was within physiological range. The systolic blood pressure (SBP) and mean blood pressure followed trends like heart rate with statistically significant but clinically insignificant fall after 15 mins. Eid E A et al[22] found that median values of MAP and HR were comparable between all three groups throughout the study duration. Gupta et al[23] found that there was no hypotension in patients of either group. Intrathecal Dexmedetomidine did not potentiate the effect of bupivacaine on blood pressure. This may be explained by the mechanism local anaesthetics affect blood pressure. Local anaesthetics reduce blood pressure by decreasing sympathetic outflow. Heat rate remained stable on lower normal side in all four groups. This may be in part due to effects of Dexmedetomidine after systemic absorption. Sympathetic blockade produced by intrathecal dexmedetomidine does not decrease blood pressure further presumably because the blockade produced by bupivacaine is nearly maximum.

In our study, only 2 (6.70 %) patients in Group D3 and Group D2 showed hypotension and 1 (3.30 %) patient in Group D1 had an episode of bradycardia and hypotension that was easily corrected by fluid and vasopressors. This incidence was statistically not significant. Haldar et al [21] found that Bradycardia was observed in both group D10 and D5 (5 vs 2 patients respectively) of which 4 patients in D10 group required atropine (0.6mg i.v.) injection whereas no patients in D5 group required active management. This side effect was found to be statistically as well as clinically significant ($p<0.05$). Level of Sedation as studied by using Modified Ramsay Sedation Score which was not more than 2 in study group.

None of the patients in all four groups any episode of apnoea or desaturation in intraoperative or postoperative period. Dexmedetomidine is known to provide excellent hemodynamic stability without causing any respiratory depression [13,14]. Similarly, incidence of postoperative nausea and vomiting was also minimal and not significant in our study groups.

Conclusion:

On the basis of the observations and results of this study we can conclude that, Dexmedetomidine fastens the onset of sensory and motor block. Also, it prolongs the duration of sensory and motor block and overall duration of analgesia in dose dependant manner. 15 μg Dexmedetomidine, the maximum dose used in our study has stable hemodynamic and respiratory profile and found to be safe option in regional anaesthesia cases.

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