 DOI: 10.18231/2394-4994.2017.0086

Effect of Intravenous Dexmedetomidine on Bupivacaine for Spinal Anaesthesia

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Abstract

Since the discovery of spinal anaesthesia, it has been used widely with different additives in local anaesthetic drugs. Vasoconstrictors like phenylephrine, opioids, neostigmine and clonidine are some of the well known agents used to prolong the duration of block; whereas hypnotic, sedative and amnesic drugs are required to reduce the discomfort. However, they affect the ventilatory mechanisms and may lead to respiratory depression, with consequent hypercarbia and hypoxemia.

A promising alternative to these drugs in anaesthesiology is the group of alpha-adrenergic agonist, which have excellent sedative and analgesic properties without respiratory depression. Clonidine an alpha 2 agonist has been used widely in the intrathecal route oral and intravenous routes to prolong the duration of spinal anagesia. dexmedetomidine, also an alpha 2 agonist, has eight times more affinity for alpha 2 receptors than does clonidine and has been used for pre-medication and as an adjunct to general anaesthesia. Various studies show that intravenous dexmedetomidine prolonged the sensory and motor blockade of bupivacaine spinal anaesthesia with good sedation and hemodynamic stability. The present study is designed to study the effect of intravenous dexmedetomidine with a loading dose of 1µg/kg and a maintenance dose of 0.5µg/kg on bupivacaine spinal anaesthesia with respect to duration of sensory and motor blockade, level of sedation and hemodynamic stability.

Keywords: Intravenous dexmedetomidine, Bupivacaine, Spinal anaesthesia

Introduction

Quincke in 1891 demonstrated a safe, predictable means of performing lumbar puncture. In 1899, August Bier used Quincke's technique to inject cocaine in order to produce operative anaesthesia, the first real spinal anaesthesia. Bupivacaine, a pipecoloxylidide derivative synthesized in 1957 by Ekenstam and introduced in clinical practice in 1963 is widely used now. It is a racemic mixture of D and L isomers and is relatively more cardio toxic compared to other local anaesthetics.[1-8]

Spinal anaesthesia, however, has certain limitations like discomfort caused by the procedure itself, limited duration of block and a patient who is wide wake and restless. Vasoconstrictors like phenylephrine, opioids, neostigmine and clonidine are some of the well known agents used to prolong the duration of block; whereas hypnotic, sedative and amnesic drugs are required to reduce the discomfort. However, they affect the ventilatory mechanisms and may lead to respiratory depression, with consequent hypercarbia and hypoxemia.

A promising alternative to these drugs in anaesthesiology is the group of alpha-adrenergic agonist, which have excellent sedative and analgesic properties without respiratory depression. Clonidine an alpha 2 agonist has been used widely in the intrathecal route[9,10,11,12] oral and intravenous routes to prolong the duration of spinal anagesia. Dexmedetomidine, also an alpha 2 agonist, has eight times more affinity for alpha 2 receptors than does clonidine and has been used for pre-medication and as an adjunct to general anaesthesia.[13,14,15] Various studies show that intravenous dexmedetomidine prolonged the sensory and motor blockade of bupivacaine spinal anaesthesia with good sedation and hemodynamic stability. The present study is designed to study the effect of intravenous dexmedetomidine with a loading dose of 1µg/kg and a maintenance dose of 0.5 µg/kg on bupivacaine spinal anaesthesia with respect to duration of sensory and motor blockade, level of sedation and hemodynamic stability.

Aims and Objectives

To evaluate the effect of intravenous dexmedetomidine on bupivacaine for spinal anaesthesia with respect to:

1. Maximum spinal level achieved
2. Time for 2 segment regression
3. Duration of sensory and motor blockade
4. Hemodynamic effects
5. Duration of Analgesia
6. Level of sedation

Materials and Method

Ethical Committee approval taken and written informed valid consent from all patients obtained. A complete pre anaesthetic assessment of all the patients was done.

Sample Size: 60 patients were enrolled for the study and the study was undertaken over 2 years period since 2011.

Inclusion criteria: Study population included patients of either sex, ASA Physical Status Class I-II patients, aged 20-60 years with weights and heights within 20%

of ideal values, scheduled for lower limb and lower abdominal surgeries.

They were divided into 2 groups C and D of thirty patients each.

Exclusion criteria: Patient not willing for study. ASA Physical status Grade 3 and 4. any bleeding disorder and patient on anticoagulants, local infection at the injection site, history of allergy to local anaesthetic, patients using alpha 2 adrenergic receptors antagonists, calcium channel blockers, angiotensin converting enzyme inhibitor, having dysrhythmias and failure of spinal anaesthesia.

All patients were kept nil per oral from 12 midnight and tablet aprazolam 0.5 mg was given on the night before surgery. Patients were randomly allocated to two groups of 30 patients each using a standard randomization code.

Dexmedetomidine group (group D): received a loading dose of 1μg /kg of dexmedetomidine over 10 minutes as soon as the patient become supine after performing spinal anaesthesia and a maintenance dose of 0.5 μg/kg/hr till the end of surgery intravenously by the intravenous infusion pump.[16]

Control group (group C): received normal saline in same calculated volume of loading and maintenance dose as in group D.[16]

Drug solution used and dosage: Dexmedetomidine was prepared in a 50cc syringe using a dexmedetomidine ampoule containing 100μg/ml diluted with normal saline to a concentration of 4 μg/ml.[27]

Bupivacaine 0.5% ampoule was used, 3.0ml of it was taken in 5 ml syringe and administered intrathecally at the rate of 1ml over 3-4 seconds.

All patients were hydrated with 500 ml Ringer's Lactate solution via an 18 gauge IV cannula in the dorsum of the hand before spinal anaesthesia.

Monitoring: Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory Rate, sedation score were measured and recorded. Standard monitors were attached.

Sensory Blockade: Onset of sensory blockade was tested by the pinprick method immediately after making the patient supine. The extent of sensory blockade was assessed at 2minute interval and highest sensory blockade achieved was noted. After that at every 15minute interval level of sensory blockade was noted. The time taken for 2 segment regression and time for regression to S 1 segment was noted.

Motor Blockade: The onset of motor blockade was assessed using Bromage scale at 2minute interval until complete motor blockade is achieved.

Modified Bromage scale

Bromage 0: the patient is able to move the hip, knee and ankle;

Bromage 1: the patient is unable to move the hip, but is able to move the knee and ankle;

Bromage 2: the patient is unable to move the hip and knee, but is able to move the ankle;

Bromage 3: the patient is unable to move the hip, knee and ankle.

Motor blockade will be evaluated at every 15 minute interval until return of full motor function.

Hemodynamic Monitoring: After performing the subarachnoid block, the patient's heart rate, systolic blood pressure, oxygen saturation and respiratory rate were recorded at 2minutes interval for first 10minutes, at 5minutes interval for next 30 minutes and at every 15minutes interval intra-operatively and in the Post Anaesthesia Care Unit(PACU).

- Hypotension is defined as a systolic blood pressure of less than 90 mmHg and was treated by increasing the rate of fluid administration and 6 mg of intravenous Ephedrine.
- Bradycardia was defined as HR < 60 beats / min and was treated with 0.6mg of intravenous Atropine.
- Blood is transfused if blood loss > 15% of patients estimated blood volume.

Sedation: Patients were observed for sedation, shivering, nausea and vomiting. Anti emetics were given as required. Sedation levels were recorded at 2, 5 and every 5minutes intra-operatively and every 15 minutes post-operatively using Ramsey Sedation Scale:

Ramsey Sedation Scale

1. Patient anxious, agitated, or restless
2. Patient cooperative, oriented, and tranquil alert
3. Patient responds to commands
4. Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6. Asleep, no response to light glabellar tap.

All sedation scores were recorded considering the time of start of infusion as time zero. Excessive sedation was defined as Ramsey Level of sedation Score greater than 4/6.

Duration of Analgesia: Post operative pain was assessed by the patient using the Visual Analogue Scale (Vas; 0 = no pain, 10 = worst possible pain) and patients with a VAS score of 3 or more received Inj. paracetamol 1grams IV. The time for the first request for post operative analgesia was recorded. The patient was discharged from PACU after sensory regression to S1 segment and Bromage scale of 0.

Follow Up: The patients were evaluated two weeks following discharge in the outpatient clinic and were assessed for any new onset of neurological impairment related to spinal anaesthesia such as back, buttock or leg pain, headache or any new neurological deficit.

Observation and results

There was no statistically significant difference in age, gender, weight, height, ASA grading, duration of

surgery, maximum level of sensory blockade in both groups.

Comparison of Time Duration of Sensory and Motor Blockade in Control and Study Group: The unpaired t-test suggests that there is significant difference (p value of < 0.001) in the two segment regression, duration of motor and sensory blockade of control and study group.

Table 1: Comparison of Sensory and Motor Blockade in Control and Study Group

Variable	Control Group		Study Group		P-Value
	Mean	SD	Mean	SD	
Two Segment Regression (in mins.)	55.83	10.67	111.77	16.31	< 0.001**
Duration of Motor Blockade (in mins)	141.27	14.96	199.73	18.52	< 0.001**
Duration of Sensory Blockade (in mins)	174.23	19.17	263.83	20.74	< 0.001**
*****: Significant at 1 % level of Significant***					

Comparison of Changes in Heart Rate: The heart rate was lower in the study group as compared to the control group and was statistically significant at 25, 105 and 120 minutes after subarachnoid block.

Table 2: Comparison of Heart Rate at Various Durations

Duration	Control Group		Study Group		p-value
	Mean	SD	Mean	SD	
0	71.27	5.00	78.80	8.39	.000
2	70.23	4.54	78.23	7.93	.004
4	69.80	4.54	78.07	7.91	.083
6	70.10	4.21	76.60	7.90	.887
8	69.21	4.22	76.40	7.85	.654
10	70.10	5.24	76.43	7.96	.493
15	72.31	4.84	76.33	8.34	1.000
20	76.00	4.14	75.33	8.20	.692
25	77.07	4.42	73.77	9.35	.033
30	77.73	6.10	73.27	9.36	.280
45	76.80	5.24	74.70	9.15	.705
60	75.93	5.88	76.70	9.34	.803
75	77.40	7.13	76.87	9.19	.031
90	80.13	5.70	75.87	8.90	.194
105	77.64	5.25	75.17	8.50	.033
120	78.57	4.86	73.89	8.25	.011
135	77.20	5.43	69.86	4.56	.
150	86.00	--	74.00	--	.086

****: Significant at 5%, **: Significant at 1% level of Significance***

Systolic Blood Pressure: The SBP was lower in the study group as compared to the control group and was statistically significant at 25, 105 and 120 minutes after subarachnoid block.

Table 3: Comparison of SBP at Various Durations

Duration (in minutes)	Control Group		Study Group		p-value
	Mean	SD	Mean	SD	
0	125.67	12.33	130.80	11.39	.099
2	126.27	10.33	128.33	9.81	.430
4	124.33	8.88	127.63	7.97	.135
6	124.47	7.27	124.73	8.75	.898
8	123.20	6.82	122.63	8.30	.774
10	122.13	6.43	120.87	9.95	.560
15	120.13	8.42	118.40	8.92	.442
20	121.20	8.33	118.53	12.18	.326

25	120.80	6.66	116.87	15.62	**.045***
30	120.80	7.46	114.07	16.34	.852
45	117.47	21.73	118.33	13.03	.544
60	120.47	8.99	121.87	8.79	.908
75	121.27	8.13	121.53	9.61	.790
90	120.87	8.48	121.47	8.90	.618
105	115.72	16.09	118.00	18.71	**.031***
120	122.86	20.18	112.25	8.91	**.003****
135	132.86	23.92	101.43	6.09	.582
150	128.00	25.46	104.00	.	.210

: Significant at 5%, **: Significant at 1% level of Significance

Mean Arterial Pressure: The mean arterial pressure was lower in the study group as compared to the control during the intra operative period.

Table 4: Comparison of DBP at Various Durations (Intra-operative)

Duration (in minutes)	Control Group		Study Group		p-value
	Mean	SD	Mean	SD	
0	79.20	7.60	78.53	6.91	.72
2	78.33	7.65	77.00	6.03	.46
4	77.67	7.28	74.67	5.81	.08
6	77.53	7.31	72.27	6.12	.00
8	76.67	7.32	71.00	7.06	.00
10	75.33	7.25	71.87	6.77	.06
15	75.07	5.75	71.13	4.13	.00
20	75.87	6.01	71.47	6.34	.01
25	75.27	6.27	72.33	6.73	.09
30	74.93	7.12	72.40	7.83	.20
45	76.40	6.75	72.47	7.06	.03
60	75.93	5.72	74.07	6.29	.23
75	76.13	5.75	73.40	6.52	.09
90	75.33	4.08	73.07	5.40	.07
105	79.60	12.92	74.21	5.91	.05
120	81.76	15.47	75.81	9.55	.13
135	91.00	20.07	77.25	4.53	.48
150	105.00	24.04	76.00	.	.95

: Significant at 5%, **: Significant at 1% level of Significance

Complications: Bradycardia was seen in 7 patients in Group D as compared to 0 in the control group **(p= <0.001).** Hypotension was seen in 4 patients in Group D as compared to 1 in the control group **(p= <0.001).**

Table 5: Comparison of MAP at Various Durations (Intra-operative)

Duration (in minutes)	Control Group		Study Group		p-Value
	Mean	SD	Mean	SD	
0	94.17	6.57	95.97	7.98	.35
2	94.31	6.25	93.99	6.81	.85
4	93.22	6.01	92.31	5.22	.53
6	93.24	6.25	89.75	6.24	**.03***
8	92.53	5.37	87.87	6.72	**.00****
10	91.13	5.76	88.48	7.25	.12
15	89.97	5.19	86.87	4.73	**.02***
20	91.02	5.29	87.29	6.78	**.02***
25	90.64	5.07	87.09	8.49	**.05***

30	90.06	6.20	86.88	8.01	**.09***
45	91.60	5.48	87.65	7.75	**.03***
60	90.95	4.86	89.99	6.38	.52
75	91.20	5.10	89.42	6.14	.23
90	89.86	4.37	89.19	5.90	.62
105	93.64	9.38	89.84	6.39	**.07***
120	93.76	12.00	90.00	7.01	.21
135	97.24	14.33	93.25	6.40	.47
150	110.67	16.03	93.33	.	.54

****: Significant at 5%, **: Significant at 1% level of Significance***

Sedation Score: The Ramsay Sedation Score was higher in the dexmedetomidine group as compared to the control group and the difference was statistically significant (p<0.001).

There was no incidence of respiratory depression in both the groups.

Table 6: Distribution according to complications

Complications	Control Group		Study Group		Total
	Frequency	Percent	Frequency	Total	
None	29	96.67%	19	63.33%	48
Bradycardia	0	0.00%	7	23.33%	7
Hypotension	1	3.33%	4	13.33%	5
Total	30	100.00%	30	100.00%	60

χ2= 10.883, DF=2, P < 0.001, significant

Rescue Analgesia Time: The duration of analgesia was significantly prolonged in the study group with a mean of 219.97+19.22 mins as compared to control group 153.00+15.52 with a p value of <0.01.

Table 7: Descriptive statistics for sedation score (intra-operative)

Group	N	Mean	SD	SE Mean	95% CI for Mean		Min	Max	p-value
					Lower Bound	Upper Bound			
Control Group	30	2.00	.00	.00	2.00	2.00	2.00	2.00	< 0.01**
Study Group	30	3.57	.82	.15	3.26	3.87	2.00	5.00	
*****significant at 1 % level of significance***									

Post Operative Monitoring: Heart rate, systolic, diastolic and mean arterial blood pressure and sedation score in both groups are comparable in post operative period.

Discussion

Intravenous dexmedetomidine has been shown to produce analgesic effects by acting at both spinal and supra-spinal levels. The analgesic effect primarily results from the inhibition of locus ceruleus at the brain stem and inhibition of nociceptive impulse transmission through both pre-synaptic and the post-synaptic alpha-2 receptors.

In our study mean time for two dermatomal regression of sensory blockade was significantly prolonged in dexmedetomidine group 111.77+16.31mins as compared to control group 55.83+10.67mins (p value < 0.001). This observation is comparable to the study done by Harsoor et al.[17] They observed that mean time to two-segment regression was 111.52+30.9 in dexmedetomidine group and 53.6+18.22 in the control group with a p value of <0.001. Significant prolongation in mean time for two dermatomal regression of sensory blockade was also reported by others, Kaya et al[18] -145 + 26 min *vs* 97 + 27 mins (p < 0.001), Tekin et al[19]- 148.3 mins *vs* 122.8 mins (p value < 0.001) in dexmedetomidine and control groups respectively.

The total duration of sensory blockade i.e. time for regression to S1 dermatome was significantly prolonged in dexmedetomidine group 263.83 + 20.74 minutes as compared to control group 174.23+ 19.17minutes (p value < 0.001) in our study. Significant prolongation in mean duration of sensory blockade in dexmedetomidine group was also reported by others Al Mustafa et al[16]- 261.5 ± 34.8 minutes *vs* 165.2 ± 31.5 minutes (p value < 0.05), Whizar-Lugo et al[20]- 208±43.5 minutes vs 137±121.9 minutes (p = 0.05), Harsoor et al[17] 222.8+123.4 minutes vs 138.36+21.62 minutes in dexmedetomidine and control groups respectively.

Thus, in our study the intravenous dexmedetomidine infusion prolonged the mean time for two segmental regression of Sensory blockade as well as the total duration of Sensory Blockade. In the present study, the time taken for motor blockade to reach the modified Bromage Scale 0 scale was significantly prolonged in dexmedetomidine group 199.73 + 18.52 minutes compared to control group 141.27 + 14.96 minutes (p value < 0.001). Delay in regression of motor block to Bromage Scale 0 was reported in previous studies, Al Mustafa et al[16] - 199 ± 42.8 min in *vs* 138.4 ± 31.3 min (p value < 0.05), Whizar-Lugo et al[20] - 191±49.8 mins *vs* 172±36.4 (P value- not significant), Tekin et al[19]- 215 mins *vs* 190.8 mins (p value < 0.001)} for dexmedetomidine group and control group respectively. Harsoor et al,[17] Elcıcek et al[22] and Hong et al[23] also found that complete resolution of motor blockade was significantly prolonged in dexmedetomidine group.

In the present study mean heart rate was found to be lower in the dexmedetomidine group than in the control group. The lower heart rate could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by Dexmedetomidine. Similar to our study the mean heart rate was significantly lower in dexmedetomidine group 70.4 as compared to control group 77.63 at 20 minutes (P value- 0.02) in the study done by Tekin et al.[19]

In the present study SBP was lower in the study group as compared to the control group and was statistically significant at 25,105 and 120 minutes after subarachnoid block. Lowest intraoperative SBP after spinal block was significantly lower in dexmedetomidine group [101.43+6.09] as compared to control group [117.47+ 21.73]. The mean diastolic blood pressure was similar in the study group as well as the control group throughout the intra operative period. The mean arterial pressure was lower in the study group as compared to the control during the intra operative period. The SBP, DBP and MAP were comparable in the post operative period in both the study and control groups. Similar observations were made by Kanazi et al[24] in their study.

In our study there was a significant difference in the number of patients with hypotension in both the groups, 13.33% vs 3.33% in dexmedetomidine and control groups respectively (p value <0.001). In contrast to study by Harsoor et al[17] who reported no significant difference between groups in the number of patients who received ephedrine to treat hypotension, the reason may be the lower bolus dose used.

In our study the infusions were continued during episodes of hypotension and/or bradycardia and the severity of these effects did not warrant stoppage of infusions at any point of time as Dexmedetomidine induced bradycardia was transient and responded to atropine whereas changes in blood pressure were without significant clinical impact and hypotension was easily managed with bolus of IV fluids and ephedrine.

In our study intraoperative Ramsay sedation scores were significantly higher in dexmedetomidine group with mean of 3.57+ 0.82, as compared to control group with mean of 2, (p value <0.001). Maximum scores in dexmedetomidine group ranged from 4-5 with a mean of 3.57. In dexmedetomidine group maximum sedation score more than 4 was achieved in 13.33% of patients (4/30) as compared to control group where maximum score was 2 with a mean of 2.00.

Thus in our study group all patients had good sedation levels that enabled their cooperation and better operating conditions for the surgeon. And also the sedation produced by dexmedetomidine differs from other sedatives as patients were easily aroused and remain cooperative. However, there was no significant difference in sedation scores between the groups in the postoperative period. Similar observations were made by Harsoor et al[17] and Kaya et al[18] in their studies.

Dexmedetomidine inhibits the release of substance P from the dorsal horn of the spinal cord, leading to primary analgesic effects.[29] Dexmedetomidine was found to be effective in providing postoperative analgesia in the present study. The time to first request for postoperative analgesic was significantly prolonged in dexmedetomidine group 219.97+19.22 minutes as compared to control group 153 + 15.52 minutes (P value < 0.001).

Conclusion

Intravenous dexmedetomidine supplementation significantly prolongs the duration of sensory block, analgesia and motor blockade after bupivacaine spinal anaesthesia. Dexmedetomidine causes decrease in heart rate and blood pressure with statistically significant incidence of bradycardia and hypotension. Dexmedetomidine induced bradycardia is transient and responds to atropine while the changes in blood pressure are without significant clinical impact, hypotension being easily managed with bolus of IV fluids and ephedrine. Further, IV dexmedetomidine supplementation during spinal anaesthesia produces satisfactory arousable sedation without causing respiratory depression.

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