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Original Article

Effects of single bolus dose of intravenous Dexmedetomidine on intrathecal hyperbaric Bupivacaine: a randomized double blind placebo controlled trial

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Abstract

Background: To prolong the effect of spinal anaesthesia into the postoperative period many pharmacological agents are being used intrathecally and intravenously. The present study was designed to assess the effects of single bolus dose of intravenous Dexmedetomidine on spinal anaesthesia and analgesia in patients undergoing lower abdominal surgeries under spinal anaesthesia with 0.5% Hyperbaric Bupivacaine.

Methods: One hundred patients posted for lower abdominal surgeries under spinal anaesthesia were randomly allocated to two groups. Group D (study group) patients received single bolus dose of 0.5mcg/kg of intravenous Dexmedetomidine and Group C (control group) received 10ml of normal saline. Variation in the onset, duration of sensory and motor level, duration of analgesia, effect on sedation and side effects were recorded.

Results: The duration of sensory block and two segment regression was significantly prolonged in Group D (189.90±7.66 minutes, 104±20.6 minutes) as compared to Group C (145.60±11.98 minutes, 75±22.5 minutes). The onset of sensory block was earlier in Group D then compared to Group C which was statistically significant. The duration of analgesia in Group D (218.8 ± 11.36 minutes) was prolonged when compared to Group C (178.6±17.96 minutes). Sedation score and incidence of bradycardia was high in Group D when compared to Group C.

Conclusion: Single bolus dose of IV Dexmedetomidine prior to spinal anaesthesia prolongs the duration of sensory block and duration of analgesia with satisfactory arousable sedation and acceptable side effects.

Key words: Bupivacaine; Dexmedetomidine; Spinal anaesthesia

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Introduction

Neuraxial administration of drugs to produce various desired effects has evolved from 18th century. To extend the effect of subarachnoid block into the post operative period, innumerable pharmacological agents are being used. Different agents, like Epinephrine, Phenylephrine, Adenosine, Magnesium Sulfate and Clonidine, have been used as adjuncts to local anaesthesia for prolonging the duration of spinal analgesia via the intrathecal[1] and intravenous route.[2]

Dexmedetomidine, the dextroenantiomer of Medetomidine, has got high specificity to alpha 2 receptors.[3] This action of it appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection and suppression of shivering.[3] The above mentioned actions has made its use in varied anesthesia and intensive care practice. Small doses of Dexmedetomidine (3 mcg) used in combination with Bupivacaine in humans in spinal anaesthesia produces a shorter onset of motor block and a prolongation in the duration of motor and sensory block with preserved hemodynamic stability and lack of sedation.[4]

There are studies showing intravenous Dexmedetomidine prolonging spinal anaesthesia with Bupivacaine when given as a bolus and continued as an infusion throughout the surgery.[5,6,7] The literature showing single bolus dose given before initiation of spinal anaesthesia are less. In our study we hypothesized the single bolus dose 0.5ug/kg of intravenous Dexmedetomidine will prolong spinal anaesthesia. In our study we compared the block characteristics along with hemodynamic changes, level of sedation and Dexmedetomidine side effects.

Materials and Methods

Randomized, prospective, double blind study was conducted on 100 patients after clearance from hospital ethical committee and obtaining informed consent from patients. Patients belonging to ASA I and II, age between 18 and 65, and posted for elective lower abdominal surgeries lasting approximately 60-120 minutes under spinal anaesthesia were included for the study. Patients with any contraindication for spinal anaesthesia, ASA III and IV, allergic to study drugs were excluded from the study.

A total of 100 patients divided in to 2 groups, Group C (control) and Group D (Dexmedetomidine) using computer randomization numbers.

All patients received sedation on the previous night in the form of Tab. Alprazolam 0.5 mg and on the day of surgery Inj Ranitidine 50 mg and Inj Ondansetron 4 mg intravenously 30 minutes before the administration of study drugs.

In the operating room, patients were briefed about the procedure. A 18G intravenous cannula was inserted on the non-dominant hand and ringer lactate was infused at a rate of 15-20ml/kg. Baseline heart rate, blood pressure, oxygen saturation and ECG were recorded. Nursing staff who was blinded in the randomization schedule prepared the drug in an identical syringe. Using a computer-generated randomization numbers, the patients were randomly divided into two groups, group D received Dexmedetomidine 0.5 µgkg and Group C received 10 ml of physiological saline, before 10 minutes of spinal anesthesia. The study drugs were premixed to a total volume of 10 ml and were administered intravenously over a period of 10 min as a single dose by an anaesthesiologist not involved in the study. For spinal anaesthesia 3ml of intrathecal 0.5% Hyperbaric Bupivacaine was used.

Vitals were recorded every 5 minutes till the end of surgery and every 15 minutes in post anaesthetic care unit. Hypotension was defined as a 20% decrease in systolic blood pressure from the baseline or less the 90 mmHg. They were treated with iv fluids and if necessary with 5 mg intravenous boluses of Ephedrine. Bradycardia was defined as a heart rate slower than 50 beats per minute and was treated with intravenous Atropine 0.5mg. Hypoxia was defined as oxygen saturation value below 90% and was treated with Oxygen.

Sensory block was assessed by loss of temperature sensation and motor blockade was determined using Bromage Scale (0 = no paralysis; 1 = unable to raise extended leg; 2 = unable to flex knee; 3 = unable to flex ankle). The level of sensory and motor blockade was checked every two min until the maximum level of the block was achieved and at five min interval subsequently. The level of sedation was evaluated throughout the study period using Ramsay Sedation Score (RSS). Duration of analgesia was considered as time from the onset of sensory block to the time of administration of first rescue analgesia, and rescue analgesia was administered when the VAS (visual analogue scale) was ≥ 3. Post operative pain was noted by using visual analogue scale 0- 10.

Statistical Analysis

The sample size of 50 in each group based on statistical power analysis was derived from previous study[5] The precision considered was α-error as 5%, β-error as 10%, to detect a 20% change in baseline blood pressure terms of hypotension, our primary goal.

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data after decoding of blinded groupsand results were expressed as mean and Standard Deviation (SD). Microsoft word and Excel have been used to generate graphs, tables etc.

student t test (two tailed, independent has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has

been performed to assess the homogeneity of variance. Chi-square or Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. A p value of less than 0.05 was considered to be statistically significant.

Results: All 100 patients completed the study without any failure. Demographic data for age, sex, height, weight, ASA class, were comparable between the two groups and were statistically insignificant (Table 1).

Table 1: Demographic Data

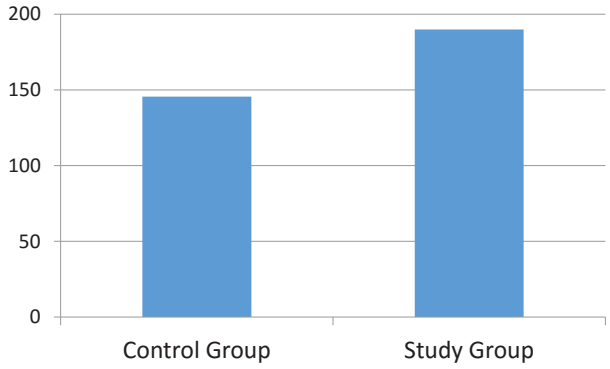
Parameters	Group C (n=50) Mean ± SD	Group D (N = 50) Mean ± SD	p Value
Age	37.82 ± 8.19	40.38 ± 7.42	0.11
Height	168.16 ± 2.96	167.90 ± 3.26	0.68
Weight	65.54 ± 11.19	69.82 ± 11.14	0.05
Sex			
Male	44	41	0.40
Female	06	09	
ASA grade			
Grade 1	38	41	0.46
Grade II	12	09	

Onset of sensory blockade was faster in Group D (1.53±1.27) compared to Group C (3.15±1.34 minutes) which was statistically significant (P < 0.001). The time required for two segment regression was significantly prolonged in Group D (104±20.6 minutes) compared with Group C (75 ±22.5 minutes), with P<0.001. There was also prolongation of duration of sensory block in Group D (189.90±7.66 minutes) compared to Group C (145.60±11.98 minutes) with P < 0.001. There was no significant difference with regards to maximum level of sensory block, onset and duration of motor block.

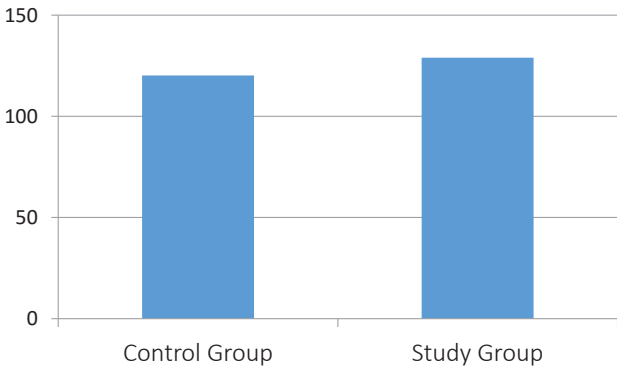
Table 2: Sensory and Motor Block Characteristics

Parameters	Group C (n=50)	Group D (n = 50)	P value
Onset of sensory block (to T10) in (min)	3.15±1.34	1.53±1.27	< 0.001*
Median maximum level of sensory blockade in (min)	T6 5.82±2.0	T6 4.91±2.4	0.044
Two segment regression (min)	75 ±22.5	104±20.6	< 0.001*
Duration of Sensory block (min)	145.60 ± 11.98	189.90 ± 7.66	<0.001**
Duration of Analgesia	178.60±17.96	218.80±11.36	<0.001**
Onset of motor Blockade in (min)	2.93±2.52	2.56±2.05	0.3906
Duration of motor blockade in (min)	120.20 ± 12.53	129.00 ± 8.21	0.7048

In Group D, the mean duration of analgesia (from the time of intrathecal deposition of drug till the administration of rescue analgesia) was 218.80±11.36 minutes. In Group C, the mean duration of analgesia was 178.60±17.96 minutes. The duration of analgesia was significantly higher in Group D when compared to Group C (p<0.001).



Graph 1: Mean duration of sensory block



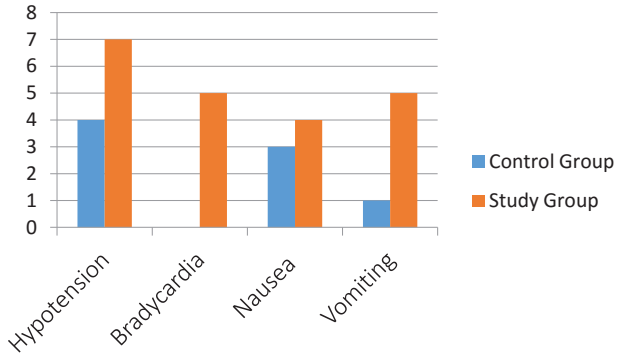
Graph 2: Mean duration of motor block

The basal hemodynamic parameters of heart rate and systemic blood pressure were comparable between the groups. In Group D, five (10%) patients had bradycardia and were treated with Injection Atropine 0.6 mg iv. In Group C, none of the patient had bradycardia. Incidence of bradycardia is statistically not significant. In Group D, seven (14%) patients had hypotension. Of these, four (8%) patients responded to intravenous fluid infusions and three (6%) patients required intravenous Inj. Ephedrine. In Group C, four (8%) patients had hypotension. Of these, three (6%) patients responded to intravenous fluid infusion

and 1(2%) patient required intravenous Inj. Ephedrine.

Table 3: Adverse Effects

Adverse Effects	Group C (n=50)		Group D (n= 50)		P value
	No	%	No	%	
Hypotension	4	14	7	14	0.525
Bradycardia	0	0.0	5	10	0.056
Nausea	3	6.0	4	8.0	1.000
Vomiting	1	2.0	5	10.0	0.204



Graph 3: Showing the incidence of side effects

Mean Ramsay sedation score was comparable in both the groups. One patient in Group D had score of more than 4. Respiratory rate, oxygen saturation and adverse effects were comparable between both the groups.

Discussion

Alpha 2 adrenergic receptor agonists have been the focus of interest for their sedatives, analgesic, perioperative sympatholytic, anaesthetic sparing and hemodynamic stabilising properties.[8] Dexmedetomidine, a highly selective alpha2 AR agonist with a relatively high ratio of alpha2/alpha1 activity (1620:1 as compared to 220:1 for clonidine), possess all these properties but lacks respiratory depression[9,10], making it a useful and safe adjunct in diverse clinical application.[3]

Pre and intra operative intravenous Dexmedetomidine prolongs the duration of sensory and motor block of local anaesthetics during spinal anaesthesia and peripheral nerve block. This mechanism is mainly attributed to its action at both spinal and supraspinal level.[11]

Different doses ranging from 0.1 to 10 µg/kg/h of intravenous Dexmedetomidine have been studied in the past. In our present study single bolous dose of 0.5ug/kg of Dexmedetomidine has been found to prolong sensory blockade. Dexmedetomidine when used in higher doses produces significant hemodynamic instability like hypotension and bradycardia.[3] Aantaa et al concluded that the optimal dose of Dexmedetomidine for single dose intravenous premedication in minor surgery appears to be in the range of 0.33 to 0.67 µg/kg.[12] Jaakola et al demonstrated moderate analgesia with a ceiling effect at a dose of 0.5 $\mu gkg^{-1.}$ Thus we selected a dose of 0.5 μgkg^{-1} in our study which was administered slowly over a period of 10 minutes prior to administer of spinal anaesthesia.[13]

In our present study the onset of spinal anesthesia was hastened but did not have any effect on onset of motor block. There was prolongation of sensory block and two segment regression but no effect on duration of motor block. This may be attributed to the study conducted by Jorm CM et al found that dexmedetomidine has an inhibitory effect on the locus ceruleus located at the brain stem.[14] Inhibition of locus ceruleus results in disinhibition of the noradrenergic nuclei and exerted descending effect on nociception in the spinal cord.[15] Similar results were seen in the study conducted by Kaya et al and Reddy et al.[16,17] There was prolongation of only sensory block when single bolous dose of dexmedetomidine was used. Whereas study conducted by Seung Hwan Jung et al, showed prolongation of both sensory and motor block with single bolous dose Dexmedetomidine.[18]

The duration of analgesia in Group D (Mean ± SD: 218.8±11.36 minutes) was more compared to Group C (Mean ± SD: 178.6±17.96 minutes) which was statistically significant. The results were also consistent with Kaya et al , Harsoor et al , Reddy et al.[16,7,17] A study by Jorm CM et al found that dexmedetomidine has an inhibitory effect on the locus ceruleus (A6 group) located at the brain stem.[14] This supraspinal action could explain the prolongation of spinal anaesthesia after intravenous Dexmedetomidine.

Dexmeditomedine action on locus ceruleus produces sedation resembling normal sleep where patients are easily arousable and co-operative. The maximum Ramsay sedation score was greater in dexmedetomidine group than in control group. Excessive sedation (Ramsay sedation score of more than 4) was observed in one patient in study group and none in the control group. Similar results have been reported in most of the studies.

In the present study, the incidence of side effects like hypotension, nausea and vomiting and treatment required for the same was comparable in both study and control groups and was not statistically significant. These findings were consistent with findings of Reddy et al.[17]

But the incidence of bradycardia was statistically non significant with p value of 0.056. These findings were consistent with Arain SR et al, Aantaa R et al studies[19,20] supporting the findings that the bradycardia effect of Dexmedetomidine is long lasting when used as a premedication drug. The lower heart rate could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by Dexmedetomidine.[21,22]

In conclusion, the results of the present study shows that, administration of single bolus dose of 0.5mcg/kg of

IV dexmedetomidine prior to SAB prolongs the duration of sensory block without prolonging motor block. It also provides satisfactory postoperative analgesia with acceptable side effects.

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