Original article

Intravenous dexmedetomidine prolongs duration of spinal analgesia: A randomized control trial

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Abstract:

Introduction: Spinal anaesthesia has become a widely used neuraxial technique particularly advantageous for infra-umbilical surgeries, as it requires a small volume of drug to produce profound, reproducible analgesia

Materials and methods : The protocol for this research was reviewed and approved by the Ethical Committee. The study design was prospective, randomized and double blinded. All ASA physical status I and II patients between ages 25 to 40yrs, posted for elective surgery amenable under spinal anaesthesia were eligible for participation.

Result and Conclusion: Intravenous dexmedetomidine (loading dose of 1µg/kg over 10 mins followed by infusion @ 0.5µg/kg for the duration of surgery) used a supplement to spinal anaesthesia significantly prolongs the duration of sensory and motor block, without causing significant hemodynamic disturbances like bradycardia or hypotension. Dexmedetomidine also provides excellent sedation without any respiratory depression.

INTRODUCTION

Spinal anaesthesia has become a widely used neuraxial technique particularly advantageous for infra-umbilical surgeries, as it requires a small volume of drug to produce profound, reproducible analgesia.Ideally, spinal anaesthesia is indicated when the surgical procedure can be accomplished satisfactorily with a sensory level that does not produce adverse patient outcomes. Hyperbaric bupivacaine is the most commonly used local anaesthetic for spinal anaesthesia with onset occurring within 10minutes and anaesthesia that lasts up to 2 to 2.5 hours which is appropriate for most intermediate to long duration surgeries, depending upon the level of sensory block needed to perform the same. [1, 2] Opioids continue to be the most preferred additive,to prolong or intensify the block and post-operative analgesia, despite theirvarious side effects like respiratory and central nervous system (CNS) depression, pruritus, nausea, constipation urinary retention, which warrants strict vigilance when used intrathecally.

Dexmedetomidine (DX) is a novel α2 adrenoreceptor agonist, an imidazole compound, pharmacologically active dextroisomer of medetomidine, latter has been used as sedative and analgesic agent for many years in veterinary medicine. [3]It is a highly selective α2 agonist with a selectivity ratio for the α2 receptor compared with the α1 receptor of 1600:1, as compared with a ratio of 220:1 for clonidine. Significant prolongation in the duration of sensory and motor block with DX used as intrathecal additive for 0.5% hyperbaric bupivacaine is well established, however literature pertaining to effect of IV administered dexmedetomidine on spinal

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anaesthesia is sparse. Severe bradycardia and moderate hypotension are the major side effects with dexmedetomidine, using the drug intravenously allows the anaesthesiologist to reduce or stop the infusion in case of a life threatening situation, while no such remedy is available if the drug has been used intrathecally. Hence the present double blinded randomized control study was performed to evaluate the effect of IV DX on spinal anaesthesia.

To evaluate effect of intravenous dexmedetomidine infusion on sensory and motor block, haemodynamic profile and level of sedation, following spinal anaesthesia.

MATERIALS AND METHODS

The protocol for this research was reviewed and approved by the Ethical Committee. The study design was prospective, randomized and double blinded. All ASA physical status I and II patients between ages 25 to 40yrs, posted for elective surgery amenable under spinal anaesthesia were eligible for participation. Written informed consent was obtained in all cases. Exclusion criteria included 1) Pregnant patients 2) patient on sedative, opioids or anti-depressant drugs 3) patient with renal or hepatic dysfunction 4) history of drug abuse 5) patient with neuropathies, seizure disorder, or psychiatric illness and, 6) known hypersensitivity to drugs used.

A sample size of 46 in each group was estimated based on the following considerations: 1) Type I error α =0.05, 2) Power of the study (1-β) 80% where type II error = 0.2%, and 3) A 20minutes difference for duration of sensory block regression to S1 level was considered to be significant. Pvalue of <0.05 was considered significant.Total 92 patients were randomized into two equal groups to receive injection Dx (Group D) or Normal Saline (Group C).

On arrival in operation room, baseline vitals were recorded and patients were preloaded with Ringer's lactate solution 10ml/kg body weight. Patient motor power and sensation to cold using alcohol swab and pain with pin prick up to T10 level was examined. Spinal anaesthesia was administered with patient in sitting position at L3-L4 level, through midline approach using a 25Gauge Quincke's spinal needle with hole pointing upwards, in case of failure of puncture at L3-L4, level was changed to L2-L3 interspace. In case of failure at both levels; the procedure was abandoned, general anaesthesia administered and such patients were excluded from the study. Hyperbaric bupivacaine(0.5%) 3ml was injected intrathecally, at the rate of 1ml/3-4seconds. Immediately following spinal anaesthesia, patients on Group D received IV dexmedetomidine; a loading dose of 1mcg/kg over 10minutes followed by 0.5mcg/kg per hour infusion tills the end of surgery. Patients in Group C received a similar bolus and maintenance infusion of normal saline.

Drug preparation: The drug was prepared by a separate anaesthesiologist and was handed over to the anaesthesiologist who performed the spinal anaesthesia, who was blinded as to which group the patient belonged.

Patient vitals were recorded immediately after spinal anaesthesia and then every 5 minutes till the end of surgery and every 15

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minutes during stay in post anaesthesia care unit (PACU), till patient was shifted to ward. Sensory block was determined using cold alcohol swab and needle prick, and was assessed every 2minutes for the first 10minutes and thereafter every 15minutes during surgery and postoperatively; time taken for sensory block to reach T10 level, two dermatomal regression and block regression to S1 level were noted. Motor block was assessed every 2minutes before start of surgery and every 15 minutes postoperatively, using Bromage scale, time to reach Bromage scale 3 and recovery from motor block to Bromage scale 0 was noted. All the durations were calculated considering time of spinal injection as time 0. The level of sedation was assessed using Ramsay level of Sedation scale, and was evaluated every 15minutes till the patient was discharged from PACU. Excessive sedation was defined as a score >4/6. Any episode of hypotension defined as systolic blood pressure <90mm of Hg or more than 20% fall from baseline value; bradycardia heart rate <50 beats/minute, were recorder and treated accordingly. Any intraoperative requirement of supplemental analgesia, time for first request for postoperative analgesic, nausea, vomiting, respiratory depression, difficulty in breathing was also recorded.

Study Tools:

Table 1: Bromage Scale

Score	
0	Patient is able to move hip, knee and ankle; no motor impairment.
1	Patient is unable to move hip, but can move knee and ankle,unable to raise either extended legs.
2	Patient is unable to move hip and knee, but can move ankle; unable to raise extended leg and flex knee.
3	Patient is unable to move hip, knee and ankle.

Table 2: Ramsay Level of Sedation

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

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RESULTS

A total 92 patients were randomized and divided into two groups to receive in dexmedetomidine (Group D or Study Group) and Normal saline (Group C or Control Group). Table 3 shows the demographic characteristics of each group. No difference was noted between the groups. ASA Physical status (I/II) : 33/13 and 30/16 in Group D and Group C respectively as shown in table 3 was comparable, type of surgery performed and duration of surgery was found to be comparable between the two groups as well.

Table 3: Demographic Variables of Patients, Type and Duration of Surgery.

Variable	*Group D (n=46)*	*Group C (n=46)*	*P value*
Age (in years)	38.91 ± 10.41	38.41 ± 9.94	NS
Weight (in KG)	57.26 ± 9.70	57.52 ± 7.33	NS
Height (in cm)	169.10 ± 11.96	170.71 ± 11.73	
ASA Physical	I – 33	I – 30	NS
Status	II – 13	II-16	
Male(M) :	M – 26	M- 29	NS
Female(F)	F – 20	F – 17	
Duration of			
Surgery (in	105 ± 14.03	106.72 ± 13.08	NS
mins)			
Type of Surgery	LA – 28	LA – 25	
	LL – 18	LL – 21	NS

LA = Lower abdomen surgery, LL= Lower Limb Surgery, NS= Non Significant (p value > 0.05)

The average duration of analgesia was significantly prolonged in Group D (Table 4). Onset of sensory block to T10, two dermatome regression of sensory block and total duration of motor block was also found to be significantly prolonged in Group D; however the time for onset of motor block corresponding to Bromage Scale 3 was found to be same in both groups (Table 4). The basal heart rate (HR) and mean blood pressure (MBP) was comparable in two groups (Table 5). The mean HR was significantly decreased in Group D, during the first hour intraoperatively and trend continued during the first hour in PACU. However there was no statistically significant difference of MBP between the groups, intraoperatively or in PACU (Table 5). Intraoperative Ramsay Sedation scores was significantly higher in Group D, the score ranged from 2-5 (maximum score of 5 in 3patients, 4 in 34 patients and 3 in 9patients), the maximum mean sedation score (3.83 ± 0.44) was achieved at 45mins; sedation score in all patients of Group C was 2. No significant difference was found in the incidence of adverse effects (bradycardia, hypotension, respiratory depression, nausea and vomiting).

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Table 4:Comparison of block for characteristic of patients

Variable	*Group D (n=46)*	*Group C (n=46)*	*P value*
Onset of sensory block T10(in seconds)	64.10 ± 4.76	119.69 ± 10.42	<0.001*
Time for two segment regression (in min)s	133.37 ± 15.78	108.47 ± 16.01	<0.001*
Duration of analgesia (in min)s	265.11 ± 24.07	163.26 ± 20.23	<0.001*
Onset of motor block (in mins)	3.65 ± 0.77	3.78 ± 0.87	NS
Duration of motor block (in mins)	281.41± 22.60	178.59 ± 20.05	NS

Values expressed as mean ± standard deviation; * stands for highly significant, NS= Non Significant (p value > 0.05)

Table 5: Comparison of hemodynamic parameters: heart rate (HR), mean blood pressure (MBP) and Ramsay Sedation Score of patients

Variables		*Group D*	*Group C*	*P value*
	Basal	81.80 ±3.84	80.59 ± 4.70	NS
	Mean intraop HR	67.28± 6.10	76.10±1.97	<0.001*
Heart Rate (beats per minute)		70±0.44	80.65±1.63	<0.001*
	Mean HR PACU			
	Basal	100.17±3.89	99.02±3.09	NS
Mean BP (mm of Hg)	***MBP***	96.49±1.46	96.20±3.16	NS
	intraop	97±0.7	97±0.11	NS
	MBP			

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	PACU			
	Mean RSS	3.02 ±0.62	2.05±0.07	<0.001*
Ramsay Sedation Score(RSS)	***MeanRSS PACU***	2.11±0.19	2±0	NS

* stands for highly significant, NS= Non Significant (p value > 0.05)

Table 6: Comparison of adverse effects between groups

Variable	*Group D (n=46)*	*Group C (n=46)*	*P value*
Hypotension	5/46	3/46	NS
Bradycardia	4/46	0/46	NS
Excessive sedation	3/46	0/46	NS
Nausea and vomiting	2/45	3/46	NS

NS= Non Significant (p value > 0.05)

DISCUSSION

Dexmedetomidine is a highly selective α2 agonist; IV dexmedetomidine administration has shown to produce analgesic effects by acting at both spinal and supraspinal levels. The analgesic effect primarily results from the inhibition of locus ceruleus in brain stem; in addition infusion of IV dexmedetomidine may result in increased activation of α2 receptors at the spinal cord leading to inhibition of nociceptive impulse transmission. The latter effect seems to be mediated through both presynaptic and the post synaptic α2 receptors. [4]There are three types of α2 receptors: A, B and C. Dexmedetomidine is a more selective α2-A receptor agonist, activation of presynaptic α2A receptors at locus ceruleus decreases nonepinephrine release and causes sedative and hypnotic effects, whereas its effect on descending medullo spinal noradrenergic pathway results in analgesia by terminating pain signal propagation.

At substansiagelatinosa of spinal cord, it decreases firing of nociceptive neurons and release of substance P, thus producing analgesia. So, dexmedetomidine has a role in modulating pain and inhibiting the transmission and perception of pain. Activation of post-synaptic α2 A receptors in CNS results in hypotension and bradycardia by decreasing sympathetic activity. Activation of post-synaptic α2 C receptors in CNS results in anxiolysis, whereas activation of post-synaptic α2-B receptors in peripheral vasculature results in transient hypertension. Dexmedetomidine has an onset of action of 30 minutes when the maintenance IV dose is used. Use of standard loading dose (1mcg/kg infused

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over 10minutes) decreases the time of onset of action.[5]In our study dexmedetomidine group was found to have faster onset of sensory block than control group similar to the study by Harsoor S *et al.* [6]mean time for two dermatomal regression of sensory blockade was found to be significantly prolonged in dexmedetomidine group (133.37 ± 15.78 mins) compared to control group (108 ± 16.01 mins). Hong *et al*[7] reported that the mean time to two segment regression was prolonged in the dexmedetomidine group (78 mins vs. 39 mins for cold and 61 mins vs. 41 mins for pinprick, in dexmedetomidine group and control group respectively). Similar observation were noted by others (Kaya *et al.*[8] 145 ± 26 mins vs. 97 ± 27 mins; Tekin*et al*.[9] 148.3 mins vs. 122.8 mins; Dinesh CN *et al*.[10]137.4 ± 10.9 mins vs. 102.8 ± 14.8 mins; in the dexmedetomidine and control group respectively). The study also demonstrated prolongation of the mean duration of analgesia in the dexmedetomidine group 265 ± 24.07 mins vs. 163.26 ± 20.23 mins in the control group, corroborating the observations by Al Mustafa *et al.*[11] 261±34.8 mins vs. 165.2±31.5 mins; Lugo *et al*[12] 208 ±43.5 mins vs. 137±121.9 min; Dinesh CN *et al.*[10] 269.8±20.7mins vs. 169.2± 12.1mins, in the dexmedetomidine and control groups respectively. Jorm*et al*. [13] found that dexmedetomidine has an inhibitory effect on the locus ceruleus located at the brain stem. This supraspinal action could explain the prolongation of spinal anaesthesia after IV dexmedetomidine. The noradrenergic innervations of spinal cord arise from the noradrenergic nuclei in the brain stem including locus ceruleus, the A5, and the A7 noradrenergic nuclei. The noradrenergic nuclei of brainstem are connected to the neurons in locus ceruleus. Axon terminals 13 of the noradrenergic nuclei reach lamina VII and VIII of the ventral horns of spinal cord. The activity of the noradrenergic neurons is decreased by agonists acting at α adrenergic receptors on the locus ceruleus cell bodies, and thus inhibition of locus ceruleus results in disinhibition of the noradrenergic nuclei and exerted descending inhibitory effect on nociception in the spinal cord.[4]

In our study there was also significant prolongation ($P < 0.001$) ofregression time for motor block to Bromage Scale 0 in dexmedetomidine group as compared to control group. Similar prolongation of motor block was also reported in previous studies [Al Mustafa *et al*. [11] 199 ± 42.8 min vs. 138.4 ± 31.3 min ($P < 0.05$),Lugo VW *et al*.[12] 191 ± 49.8 min vs. 172 ± 36.4 min (*P* value not significant), Tekin*etal*.[9] 215 min vs. 190.8 min ($P < 0.001$), Dinesh CN *et al*.[10] 220.7 ± 16.5 min comparedvs. 131.6 ± 10.5 min ($P < 0.001$); in dexmedetomidine group and control group,respectively]. Elcicek*et al*. [14]also found that complete resolution ofmotor blockade was significantly prolonged in the dexmedetomidine group, while using hyperbaric ropivacaine for spinal anaesthesia. Contrary tothe above studies, Kaya *et al*. [8] reported no significant prolongation in the duration ofmotor block in the dexmedetomidine group compared to the control group. The mechanism of motor block is unclear, there is some evidence that clonidine results in direct

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inhibition of impulse conduction in the large, myelinated Aα fibres and the 50% effective concentration (EC50%) measured approximately 4-folds of that in small, unmyelinated C fibres.[15,16] This explains the comparatively less prolongation of motor block compared to sensory block, as conduction of motor nerve fibres was less inhibited than sensory nerve fibres at the same concentration of clonidine. The same process might be applied to dexmedetomidine, and would explain the more sensory than block prolongation and discrepancies in the results of regression of motor block seen during some studies.

Hemodynamic response following dexmedetomidine infusion depends upon the speed of infusion. A sequence of transient hypertension with reflex bradycardia, followed by hypotension is seen with higher does and rapid infusion. [17,18]The decrease in heart rate associated with dexmedetomidine infusion can be attributed to the decreased level of circulating catecholamine resulting from decreased sympathetic outflow. In our patients the heart rate decreased significantly after starting loading dose of dexmedetomidine infusion and the heart rate continued to be lower even during stay in PACU. Similar decrease in heart rate was noticed in other studies as well. Contrary to previous studies which showed bradycardia as major side effect[7,10,12,14] (incidence 30-40%) in patients receiving dexmedetomidine, only 4 patients of dexmedetomidine group developed bradycardia which needed treatment with atropine. Harsoor*et al.*[6] and Kaya *et al.* [8] also did not found bradycardia significant, but they used lesser dose of dexmedetomidine than used in our study.Previous studies have shown hypotensive effects of dexmedetomidine persist in the intraoperative as well as in the postoperative period. Elicecke*t al.* [14] reported significant decrease in mean arterial pressure in dexmedetomidine group. Contrary to the above observation Tekin*et al.* [9]and Al Mustafa *et al.* [11] reported no significant difference in mean arterial pressure between groups. In our study, there was a decrease in mean BP in both groups with no significant difference. 5 patients in dexmedetomidine group and 3 patients in control group developed hypotension which needed intervention.

Dexmedetomidine produces sedation by its central effect and it seems to be dose dependant.[19] In our study excessive sedation was observed in 3 patients in dexmedetomidine group. Although respiratory rate was lower in dexmedetomidine group, it was not clinically significant enough to be considered as respiratory depression; oxygen saturation was maintained well in either groups. Hong *et al.*[7] reported desaturation in two patients which can be attributed to advanced age of patients selected in the study. No significant difference in the incidence of nausea, vomiting was observed in this study.

CONCLUSION:

Intravenous dexmedetomidine (loading dose of 1µg/kg over 10 mins followed by infusion @ 0.5µg/kg for the duration of surgery) used a supplement to spinal anaesthesia significantly prolongs the duration of sensory and motor block, without causing significant hemodynamic

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disturbances like bradycardia or hypotension. Dexmedetomidine also provides excellent sedation without any respiratory depression.

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