Original article:

Comparison of intravenous dexmedetomidine with intravenous clonidine for prolongation of spinal anaesthesia: A randomized double-blind study

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Abstract:

Background: Clonidine and dexmedetomidine prolong the duration of subarachnoid block (SAB) when given intrathecally. Reports also suggest that they have the same effect when given intravenously.

Aim: Our objectives were to compare and evaluate effect of intravenous dexmedetomidine and clonidine on sensory, motor and autonomic components of bupivacaine SAB and the level of sedation.

Methods: In this prospective, randomized, double-blind placebo-controlled study, 90 patients of American Society of Anaesthesiologists status I or II, scheduled for variety of surgeries under SAB, were randomly allocated into three groups of 30 each. Group D received dexmedetomidine 1 µg/Kg ,followed by 0.5 µg/kg/h drip until end of surgery. Group C received clonidine 2 µg/ kg followed by 0.9% saline drip until end of surgery. Group S was managed with a 0.9% saline infusion similarly. The drugs were given as bolus over 20 minutes, 20 minutes after SAB. Duration of postoperative analgesia, sedation scores and side effects were recorded. Data was analyzed using analysis of variance or Chi-square test, and value of $P < 0.001$ was considered statistically significant.

Results: Sensory block of SAB was prolonged with minimal effect on motor block. Total duration of sensory analgesia of SAB was significantly prolonged in Group D i.e. 378 ± 83.60 min vs. 291.00 ± 77.653 min in Group C, $P < 0.001$ vs. 262± 85.557 min in group S. The maximum Ramsay sedation score was 3 in both groups D and C.

Conclusion: Intravenous dexmedetomidine prolongs the duration of sensory block in SAB more than clonidine.

Keywords: Dexmedetomidine, Clonidine, Intravenous Administration, Postoperative Pain, Conscious Sedation, Anaesthesia, Spinal.

Introduction:

Spinal anaesthesia or sub-arachnoid block (SAB) involves injection of a local anaesthetic into the subarachnoid space. SAB with 0.5 % hyperbaric bupivacaine is commonly used for surgeries below umbilicus lasting for about 2 hours. [1] Adjuvants are added to local anaesthetics to prolong the duration of analgesia and anaesthesia. [2] Clonidine, a α_2 adrenergic agonist, has been used widely with SAB to prolong the sensory and motor blockade without significant adverse effects. [3] Dexmedetomidine, a highly selective α2 adrenergic agonist is reported to have synergistic interaction with local anaesthetics. [4] The use of intrathecal adjuvants prolongs the duration of SAB. [5] SAB with or without intrathecal adjuvants is a onetime process. On the other hand intravenous adjuvants can be given continuously as an infusion or as a bolus. The duration of surgery can increase due to multiple factors. Intravenous adjuvants can synchronise the duration of surgery with the duration of prolongation of spinal anaesthesia. As compared to intravenous clonidine there are very few studies regarding the effects of intravenous

dexmedetomidine on the duration of sensory and motor block of SAB. [6] Fewer studies have compared this effect of dexmedetomidine with that of clonidine. Our objectives were to compare and evaluate effect of intravenous dexmedetomidine and clonidine on autonomic, sensory, and motor components of bupivacaine SAB, the level of sedation and side effects if any. Different surgeries requiring sensory block at different cephalic dermatomes were used.

Materials and methods:

After the local ethics committee approval, a prospective, double-blind, placebo controlled study was conducted to compare the effects of intravenous dexmedetomidine and clonidine on bupivacaine spinal anaesthesia. The study was carried out from October 2012 to October 2014. A total of 90 patients were enrolled which were of both sexes, American society of anaesthesiologist (ASA) grade I and II, age between 20 to 55 years and weight between 40 to 70 kilograms. After thorough pre-anaesthetic evaluation, patients with history of alcohol or drug abuse, cardiac diseases, hypertension, chronic obstructive respiratory disease, metabolic or endocrinal disorders, neurologic, hepatic or renal dysfunction, coagulation disorder, allergy to local anaesthetics, infection at the site of lumber puncture, deformed spine or refusal to technique and pregnancy were excluded from the study. Written informed consent was taken. All surgical procedures below the umbilicus like abdominal & vaginal hysterectomies**,** diagnostic laparoscopies, inguinal hernias and lower limb orthopaedic surgeries were included in our study. Patients were monitored with continuous electrocardiogram (ECG), non-invasive blood pressure (NIBP) and pulse oximetry (SpO_2). After preloading with 10ml/kg ringers lactate solution, with the patients in sitting position, under all aseptic precautions, a midline lumbar puncture was performed using a 25 G spinal needle. Depending on height, weight and surgery, the dose of 0.5% hyperbaric bupivacaine was injected. After computerised randomisation, all 90 patients were allocated into one of the following three groups of 30 each.

Group D (n = 30) received intravenous dexmedetomidine as a bolus of 1 µg/Kg over 20 minutes(mins) started 20 minutes after the SAB, followed by 0.5 µg/kg/h dexmedetomidine drip until end of surgical procedure.

Group C (n = 30) received intravenous clonidine as a bolus of 2 µg/ kg over 20 minutes, started 20 minutes after the SAB, and followed by a 0.9% saline drip until the end of surgery.

Group S (n = 30) were managed with a 0.9% saline infusion started 20 minutes after the SAB followed by a 0.9% saline drip until the end of surgery.

All patients received intravenous fluids as needed, as well as oxygen via ventimask. Patient and anaesthesiologist were double blinded to the drug administered. The sensory block was assessed by pinprick method at 2 min intervals until the maximum cephalic level of the block was achieved and at 5 min interval until the level is fixed; half hourly till 5 hours and hourly thereafter. Similarly, the motor blockade was evaluated bilaterally by modified Bromage scale- (0-3): 0: Full movement, no power impairment, 1: Unable to raise extended leg at hip, 2: Unable to flex the knee, 3: No motor activity. [7] Onset of motor block was considered when complete loss of motor power was achieved. The onset time of sensory and motor blockade at the respective dermatomes depending upon surgery and maximum cephalic dermatome level of sensory block was calculated. The regression time to reach S1 sensory level and time taken to achieve complete recovery from motor blockade were also assessed. Total duration of analgesia was defined as time from administration of subarachnoid block

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until the first complaint of pain. Intramuscular injection diclofenac was used as rescue analgesic. ECG, SpO_2, NIBP, and heart rate (HR), were recorded before and after subarachnoid block at 3 min interval until 20 min and then regularly. Hypotension (defined by systolic pressure <90 mmHg) was treated with intravenous fluids and vasopressors (mephenteramine), if required. Bradycardia (HR< 50 beats/min) was treated with glycopyrrolate. Respiratory depression was defined as a respiratory rate <12 breaths /min. The level of sedation was evaluated using Ramsey Sedation Score (RSS). 1: Patient anxious, agitated or restless; 2: Patient co-operative, oriented and tranquil; 3: Patient responds to verbal commands; 4: Patient asleep with brisk response; 5: Patient asleep with sluggish response; 6: Patient asleep with no response.

Intra-operatively pain, respiratory depression, nausea, vomiting and shivering or any other drug induced side-effects were noted and managed accordingly. All intra-operative monitoring and management of complications was done by an anaesthesiologist blinded to the above randomisation.

Sample size calculation was based on a previous study [8] for which we assumed a standard deviation (SD) of 24 min in time to sensory regression of two dermatomes, an α-error of 0.05, and a β-error of 0.2. To show a 20% difference in sensory regression of two dermatomes, at least 27 patients per group were needed, so we selected 30 patients per group. The data were analyzed statistically using SPSS (Statistical package for social sciences) version 20.0, parametric testing was done using one-way analysis of variance (ANOVA), intergroup comparison was done with Tukey's test used and categorical data were analyzed using the Chi-square test/Fisher's exact test (cell frequency < 5). Quantitative Data was presented as mean ± SD and Qualitative data variables were presented in (percentage). Mann-Whitney U test was used to find the group wise comparison for skewed data (Duration of sensory). The values of $P <$ 0.001 were considered to indicate statistical significance.

Results:

The study was successfully completed on all 90 patients. All patients were co-operative during evaluation of sensory and motor block and sedation. The demographic data were comparable between the groups for age, weight, height, sex, type of surgery, ASA physical status and duration of surgical procedures. [Table no. 1 and Table no.2]

The basal hemodynamic parameters of HR and systolic blood pressure were comparable between the three groups. The trend of heart rate and systolic blood pressure in Group D and Group S shows no significant difference. [Table no. 3 and Table no.4]

With reference to table no.3 and graph no. 4: Intra-operatively, there was statistically significant decrease in HR in patients of Group C in 3rd and 4th hour. But this decrease was not clinically significant as bradycardia was not noted.

With reference to table no.4 and graph no. 5: Intra-operatively, there was statistically significant decrease in systolic blood pressure in patients of Group C in 2nd to the 4th hour. But this decrease was not clinically significant as hypotension was not noted.

There was no significant difference in the mean onset time of sensory analgesia at respective dermatomes and onset of motor blockade between the groups.

The maximum level of cephalic spread of sensory blockade was comparable between the groups but it was not exactly the same considering different cephalic dermatomes required for different

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surgeries. The time required for two segment recession could not be calculated for every case because of the same reason. But the total duration of sensory analgesia can be calculated which was significantly prolonged in Group D 378 ± 83.60 min vs. 291.00 ± 77.653 min in Group C, $P < 0.001$ vs. 262± 85.557 min in group S. The p value is <0.001 as calculated by the Kruscal Wallis test [Table no.5]

The time required for complete fixation of motor blockade was comparable in all three groups which was about 20 mins. Maximum score of modified Bromage scale of 3 was achieved at about 20 mins and the score remained the same for about 180 mins in all the three groups. There is no statistically significant difference in the time taken for complete regression of motor blockade in any of the group [Table no.7]. The motor blockade was of shorter duration in all the three groups when compared with sensory analgesia.

The maximum RSS of 3 was achieved after 120 mins in patients of Group D and Group C. RSS was comparable in both the groups in the post-operative period. The RSS was higher (arousable sedation) in patients of Group D and Group C than Group S and it was statistically significant [Table no.8].

As seen from Graph no.8, there is a statistical difference between respiratory rate (RR) of Group C and the other groups. RR of Group D and Group S showed a similar trend. But respiratory depression was not observed as the RR never decreased less than 12 in any of the groups.

No significant complications occurred after use of intravenous infusion of dexmedetomidine and clonidine in our study and no patient had any neurological symptoms. The adverse events were as follows [Table no.9]:

Nausea and vomiting were managed appropriately. Shivering was incidentally found to be significantly less in Group D and Group C than Group S.

Table1: Comparability of gender

S. no.	Gender	Group			Total
		D	C	S	
1	Male	19	20	19	58
2	Female	11	10	11	32
Total		30	30	30	90

Table 2: Comparability of age: (p value-0.986)

Group	N	Mean age	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
D	30	36.03	8.652	1.580	32.80	39.26	22	54
C	30	36.37	9.416	1.719	32.85	39.88	21	55
S	30	36.03	8.652	1.580	32.80	39.26	23	53
Total	90	36.14	8.815	.929	34.30	37.99	21	55

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Table 3: Hemodynamic Parameters – Heart Rate (per min)

Time	Group	Mean	Standard deviation	Minimum heart rate	Maximum heart rate	P value
150 mins	D	76.53	10.490	60	90	0.003
	C	69.00	6.883	62	80	
	S	76.53	10.490	60	90	
180 mins	D	77.47	8.253	64	88	< 0.001
	C	67.73	5.452	62	78	
	S	77.47	8.253	64	88	
3.5 hour	D	78.27	10.262	64	94	< 0.001
	C	65.73	5.452	60	76	
	S	78.27	10.262	64	94	
4 hour	D	77.13	9.864	64	96	< 0.001
	C	69.07	4.093	62	74	
	S	77.13	9.864	64	96	
5 hour	D	75.20	7.941	64	90	0.533
	C	73.47	4.032	70	78	
	S	75.20	7.941	64	90	

Table 4: Hemodynamic Parameters: Systolic Blood Pressure (mm of Hg)

Time	Group	Mean	Standard deviation	Upper limit	Lower limit	P value
60 mins	D	120.13	7.682	106	134	< 0.001
	C	113.00	6.052	104	120	
	S	119.67	7.667	106	134	
	Total	117.60	7.814	104	134	
90 mins	D	120.07	7.134	108	132	< 0.001
	C	109.20	4.999	104	118	
	S	119.67	7.260	108	132	
	Total	116.31	8.216	104	132	
120 mins	D	120.20	8.177	104	134	< 0.001
	C	107.20	3.044	102	110	

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	S	119.33	8.491	104	134	
	Total	115.58	9.160	102	134	
150 mins	D	118.87	7.731	106	136	< 0.001
	C	107.20	2.759	102	110	
	S	118.60	8.105	106	136	
	Total	114.89	8.560	102	136	
180 mins	D	118.60	8.854	104	134	< 0.001
	C	108.20	2.310	102	110	
	S	118.53	8.928	104	134	
	Total	115.11	8.798	102	134	
3.5 hour	D	118.93	9.421	106	136	< 0.001
	C	108.60	1.831	104	110	
	S	119.07	9.508	106	136	
	Total	115.53	9.153	104	136	
4 hour	D	118.60	9.069	108	138	0.014
	C	113.20	5.910	106	120	
	S	118.67	9.041	108	138	
	Total	116.82	8.453	106	138	

Table 5: Duration of sensory block (minutes)

Group	N	Mean	Std. Deviation	Median	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
D	30	378.00	83.600	240.000	346.78	409.22	240	480
C	30	291.00	77.653	210.000	262.00	320.00	210	480
S	30	262.00	85.557	180.000	230.05	293.95	180	360

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Table no.6: Matrix of P values of sensory block

	Group D	Group C	Group S
Group D	-	< 0.001	< 0.001
Group C	-	-	0.032
Group S	-	-	-

Table no. 7: Bromage scale

Time (mins)	Bromage scale		
	Group D	Group C	Group S
20	3	3	3
30	3	3	3
45	3	3	3
60	3	3	3
90	3	3	3
120	3	3	3
50	3	3	3
180	3	3	2
3.5 hour	2	2	2
4 hour	2	2	2
5 hour	1	1	1
6 hour	0	0	0
8 hour	0	0	0
10 hour	0	0	0

Table 8: Sedation scores (Ramsay Sedation Score)

Time	Group D RSS	Group C RSS	Group S RSS	P value
20 mins	2	2	1	< 0.001
30 mins	2	2	2	0.005
45 mins	2	2	2	0.016
60 mins	2	2	2	0.001
90 mins	2	2	2	0.999
120 mins	3	3	2	< 0.001
150 mins	3	3	2	< 0.001
180 mins	3	3	2	< 0.001
3.5 hours	2	3	2	< 0.001
4 hours	2	2	2	< 0.001

5 hours	2	2	2	< 0.001
6 hours	2	2	2	< 0.001
8 hours	2	2	2	< 0.001
10 hours	2	2	2	< 0.001

Table 9: Adverse Events

Variables	Group D	Group C	Group S	P value
Nausea	2	3	2	0.999
Vomiting	1	2	2	0.999
Shivering	1	1	7	0.011

Discussion:

Adjuvants, like catalysts, potentiate the action of local anaesthetics when given simultaneously. Various intrathecal and systemic adjuvants to local anaesthetics have been found to improve the quality and the duration of spinal block. In spite of side effects like pruritis and respiratory depression, opioids are one of the most widely used adjuvants.Alpha 2-adrenergic agonists act by a central and a peripheral mechanism. According to the former, alpha 2-adrenergic agonists act at spinal level and supraspinal level. At spinal level they act on laminae VII, VIII of the ventral horns. Locus coeruleus and dorsal raphe nucleus are the supraspinal sites. The most accepted mechanism is the release of acetylcholine and nitric oxide. A peripheral mechanism has also been proposed. These different mechanisms help us to give these drugs through different routes and still have the same effect. Dexmedetomidine has sedative, analgesic and anaesthetic properties. Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist with α_2:α_1 binding ratio of 1620:1 compared to 220:1 for clonidine. [9] Due to this greater selectivity, dexmedetomidine is more effective than clonidine as sedative and analgesic.

We have given dexmedetomidine slowly in our study as it is recommended to administer dexmedetomidine over more than 20 min.Rapid intravenous administration might produce sudden hypertension. [10]This is attributed to initial stimulation of α-2B receptors present in vascular smooth muscles. This hypertensive episode settles once there is decrease in central sympathetic outflow. [11] Most of the studies have noted bradycardia with varying incidence sometimes requiring treatment. Bradycardia is attributed to reflex response for transient hypertension during initial part of infusion. Subsequent decrease in heart rate is due to decrease in central sympathetic outflow. But no biphasic changes or significant hemodynamic variability occurred as dexmedetomidine 1µg/kg was given over 20 min.

Hyperbaric bupivacaine takes up to 30 minutes to be fixed on the spinal neural structures. If alpha2-adrenergic agonists are given intravenously before or during the first 30 minutes after the local anesthetic injection, they would extend the duration of spinal anesthesia. According to the data in table 5 duration of sensory analgesia(sensory component of SAB) was significantly prolonged in Group D (378 ± 83.60 min vs. 291.00 ± 77.653 min in Group C, $P < 0.001$ vs. 262± 85.557 min in group S). The median time of duration of sensory block was 240 mins, 210 mins and 180 mins in group D, C, and S respectively. Thus, dexmedetomidine and clonidine were able to slow the recession of sensory level. Studies by Al Mustafa *et al.* [12] and Reddy *et al.*

[13] also observed similar findings in their study. In another study observing the effect of dexmedetomidine infusion on spinal anaesthesia with ropivacaine, it was observed that dexmedetomidine bolus of 1 mcg/kg followed by infusion at 0.4 mcg/kg/h prolonged the duration of sensory and motor regression. [14] Recently, administration of a single bolus of 1 mcg/kg, [15] and 0.5 mcg/kg, [16] also were reported to prolong the duration of analgesia and sensory blockade.

The duration of motor block was not affected by dexmedetomidine and clonidine. In our study, no significant difference was observed between the three groups. Kaya *et al*. [16] have used a single dose of 0.5 µg/kg dexmedetomidine and reported no effect on duration of motor block. We did not find any enhanced effect on motor block with clonidine also. This result has been explained by direct inhibition of impulse conduction in large, myelinated A-alpha fibers by clonidine. The EC50 (50% effective concentration) of clonidine in these fibers is approximately 4-fold of that in small, unmyelinated C fibers.

Dexmedetomidine and clonidine are themselves sedatives so the need of intra-operative sedation is eliminated, thus providing better conditions for the surgeon and the patients. Our study has demonstrated effective sedation score of about 3 as observed by Ramsay sedation scale. Respiratory rate and oxygen saturation were maintained equally well in all the patients. The results of our study validate minimal to none respiratory depression following dexmedetomidine and clonidine .This sedation differs from other sedatives, as patients are easily arousable and remain co-operative.

Regional anaesthesia produces vasodilatation, which facilitates core to peripheral redistribution of heat and cause shivering.Anti-shivering action of dexmedetomidine and clonidine is mediated by its central α-2 activity. Both decrease the thermoregulatory threshold for vasoconstriction and shivering. In our study, only one patient of Group D and one patient of Group C showed intra-operative shivering. 7 patients in Group S showed shivering. The intensity of shivering was less in group C and D than group S.

Intravenous dexmedetomidine was more effective than clonidine at prolongation of the duration of sensory block of spinal anaesthesia with 0.5% hyperbaric bupivacaine. Both provided arousable sedation with stable cardiovascular parameters and without respiratory depression. Both significantly decreased the incidence of post-spinal shivering.

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