Comparison Of Duration Of Analgesia, Sensory And Motor Blockade, And Intra-Operative Haemodynamic Changes Caused By Intrathecal Bupivacaine, Bupivacaine Plus Clonidine, And Bupivacaine Plus Dexmedetomidine In Spinal Anaesthesia

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Abstract
Background: Spinal anesthesia is commonly used for surgery and early analgesic intervention is often required to manage postoperative pain control after spinal anesthesia with only local anesthetics. Several adjuvants, such as Clonidine and Dexmedetomidine have been studied to prolong the effect of spinal anesthesia.
Material And Methods: This was a randomized, double-blinded, prospective, and observational study done on patients who were planning to undergo elective orthopedic surgeries under spinal anesthesia. The enrolled patients were randomized into three groups of 50 each (n=50) who then received 3.0ml of 0.5% Bupivacaine (group B), 3.0ml of 0.5% Bupivacaine mixed with Clonidine 30µg (group C) and 3.0ml of 0.5% Bupivacaine plus 5µg Dexmedetomidine (group D).
Observation And Results: As compared to group B patients, group C and group D had a statistically significant prolonged duration of motor and sensory block. Moreover, there was no hemodynamic instability that required intervention.
Conclusion: In conclusion, 5µg Dexmedetomidine seems to be an attractive adjuvant to spinal bupivacaine, even better than clonidine in surgical procedures.

Keywords: Spinal Anaesthesia, Bupivacaine, Dexmedetomidine, Clonidine

Introduction

Spinal anesthesia is commonly used for surgery because of its ease of administration. Spinal anesthesia with only local anesthetic has a short duration of action. The short duration of action creates lots of difficulties for the surgeon, anesthesiologist, and patient. It limits the type of surgeries that can be performed with spinal anesthesia. [1] Many times, it also warrants conversion to general anesthesia midway between surgeries due to the wearing-off effect of spinal anesthesia. Moreover, early analgesic intervention is required to manage postoperative pain control after spinal anesthesia with only local anesthetics. Hence several adjuvants such as Clonidine, Dexmedetomidine, Midazolam, Opioids, Neostigmine, and Magnesium sulfate, have been studied to prolong the effect of spinal anesthesia. Alpha 2–Adrenoceptors which are the site for the action of Clonidine and Dexmedetomidine are located on primary afferent terminals of both peripheral and spinal endings, on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei implicated in analgesia thus supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites. [2]Clonidine and Dexmedetomidine have been repeatedly demonstrated to prolong sensory and

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motor block when used intrathecally with local anesthetics. Clonidine and Dexmedetomidine have also been known to affect blood pressure in a complex fashion after intrathecal administration, because of opposing actions at multiple sites.[3] The combination of Clonidine or Dexmedetomidine also allows for a reduction in the total dose of the local anesthetic used, which translates into better hemodynamic stability intraoperatively. Clonidine and Dexmedetomidine have also been shown to have significant analgesic effects in the postoperative period much after the regression of the motor blockade which allows for early and pain-free ambulation.[4] because of these facts, this study is planned to compare the effects of Dexmedetomidine and Clonidine on the duration of analgesia, motor and sensory blockade and the intraoperative hemodynamic profile when mixed with Bupivacaine. This study also aims to ascertain the safety of these drugs for use in routine practice in the hospital.[5]

Material And Methods: This was a randomized, double-blinded, prospective, observational study done in the Department of Anaesthesiology, Government Thiruvarur Medical College and Hospitals, Thiruvarur, a tertiary care teaching hospital, between September 2021 to August 2022. The study was done on patients who were planning to undergo elective orthopedic surgeries under spinal anesthesia. A total of 150 patients planned for elective orthopedic surgeries under spinal anesthesia in the age group of 15 to 45 years and belonging to ASA Physical Status I and II were enrolled for the study. Patients less than the age of 15 years and more than 45years, Patients with co-morbid conditions and who were using α_2-adrenergic receptors antagonists, calcium channel blockers, angiotensin-converting enzyme inhibitors, Patients with psychiatric illness and neurologic diseases, Patients belonging to the class ASA Physical Status III–V were excluded from this study. The enrolled patients were randomized into three groups of 50 each (n=50) using a random number table. **The first group (Group B)** received only 3.0ml of 0.5% Bupivacaine (Heavy). **The second group (Group C)** received 3.0ml of 0.5% Bupivacaine (Heavy) mixed with Clonidine 30μg. **A third group (Group D)** was administered 3.0ml of 0.5% Bupivacaine (Heavy) mixed with 5μg Dexmedetomidine. These solutions were diluted with

0.9% saline solution to a total volume of 3.5ml and were prepared by a person not involved in the patient's care. The anesthesiologist and the patients were blinded to the study solutions. After obtaining approval from Institute's ethical committee and getting written informed consent, all patients were given a Tablet of Diazepam 5mg per oral given at 2200 hours the night before surgery. Before intrathecal injection, all patients underwent standard monitoring (GE Dash 3000), including an electrocardiogram (5 lead), non-invasive blood pressure, pulse oximeter, and baseline vital parameters were noted. An intravenous (IV) access with a 16-gauge IV cannula (B. Braun Medical, India Pvt. Ltd) was established in all patients and they were preloaded with 500ml of HES and 500ml of Ringer Lactate. Spinal anesthesia was performed with the patient in the sitting position, using a 25-gauge LP needle (B. Braun Medical, India Pvt. Ltd) with a midline approach at L_3–L_4 interspace. After intrathecal injection, patients were immediately placed in the supine position with their head elevated for 5 minutes after which, they were placed in the required position for the start of the surgery. Heart rate and non-invasive arterial blood pressure were measured every 3 minutes for 15 minutes and then every 15 minutes till 2 hours of surgery and thereafter every 30 minutes till completion of the surgery, whereas peripheral oxygen saturation was monitored continuously by a pulse oximeter. The intensity of pain was assessed using a 10-cm Visual Analog Scale. The patient was asked to point to the position on the line between the faces to indicate how much pain they were currently feeling. The far-left end indicated 'No Pain' and the far-right end indicated 'Worst pain ever'. Once the patient had indicated how much pain they had, the clinician reviewed the reverse side of the ruler, which indicated a number 0-10. The number that correlated with the position on the VAS the patient pointed to was the pain rating recorded. The study also compared the duration and regression of sensory and motor block in the post-operative period till the time the regression of the block was complete. The regression of sensory block was determined by a pin-prick test in the mid-clavicular line bilaterally.

Motor block was assessed using the Modified Bromage Scale.

Modified Bromage Scale

| Grade	Definition
0	No motor block
1	Inability to raise extended leg; able to move knees and feet
2	Inability to raise the extended leg and move knee; able to move feet
3	Complete block of motor limb

The data was collected every hour till there was complete regression of block. During surgery, the Ringer Lactate solution was infused depending on the deficit and maintenance required. Additional IV fluids (crystalloids, colloids, and blood) were administered as dictated by blood loss and hemodynamic instability. The blood loss of more than 500ml was replaced with packed red blood cells if hemoglobin was less than 90g/L. We defined clinically relevant hemodynamic instability as a decrease of 30% or more in mean arterial pressure from the baseline value. These patients were treated with 300ml of additional fluids. An incremental IV bolus of 6mg ephedrine (Claris Life sciences, Inc., Gujarat, India) was given if there was no response in mean arterial pressure. Clinically relevant bradycardia was defined as a decrease in heart rate of less than 50/minute or a 20% decrease from the initial value and was treated with 0.6mg atropine IV, as needed. The three groups were compared for their efficacy to achieve maximum sensory and motor blockage, time is taken to achieve a designated level of blockage, success in achieving the designated level of blockage, and like variables including intra-operative and post-operative complications and use of analgesics. Chi-square test, ANOVA, "t"-test, and paired "t"-test was used for Univariate analysis. The result was measured in terms of the significance of association at a 95% confidence level i.e., "p" value less than 0.05.

Observations And Results

A total of 150 patients were enrolled in the study. The age of the patients ranged from 18 to 45 years. The mean age of the patients was 30.87 ± 8.5 years. The distribution of age was normal with a slight skew to right. The patients ranged from 34 to 90kgs. The mean weight of the patients was 66.13 ± 10.35 kgs. The distribution was normal with a slight skew to the right. 57 % of the patients enrolled in the study were males and 43.3 % of the cases were females. Majority of the cases enrolled in the study were knee disorders and the rest were fracture femur, tibia, etc.

Fig 1: Distribution Of Cases
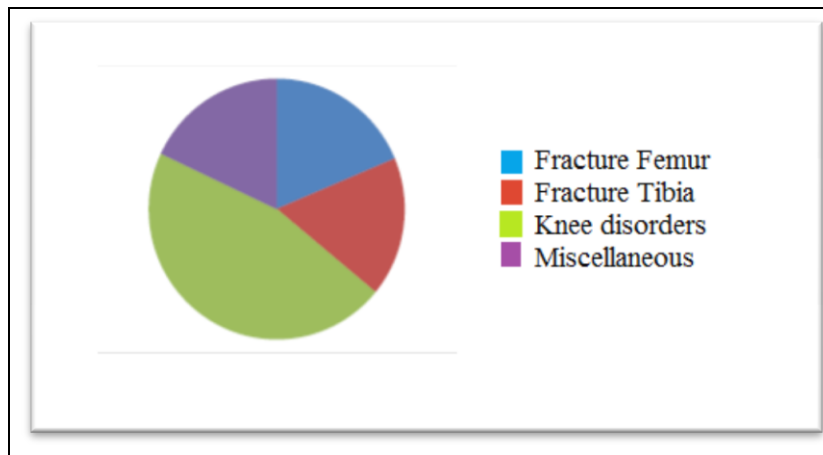
54.7% of the patients included in the study were of ASA Physical Status I and the remaining 45.3% of patients were in ASA Physical Status II. Group B showed a mean motor blockade of 166.5 ± 46.6 minutes, assessed using the Modified Bromage Scale. The motor block ranged from 84 minutes to 278 minutes. Group C showed a mean motor blockade of 243.84 ± 58.1 minutes. The motor block ranged from 111 minutes to 398 minutes. Group D showed a mean motor blockade of 408 ± 82.9 minutes. The motor block ranged from 245 minutes to 678 minutes. Of the three groups of patients, Group D had the longest duration of mean motor blockade followed by Group C whereas Group B had the least duration of mean motor blockade. Moreover, the difference in duration of mean motor blockade among the three groups of patients was statistically significant with unpaired student test i.e., "p" value less than 0.001

Table No: 01- Comparison Of Mean Duration Of Motor Block In Minutes Assessed Using The Modified Bromage Scale

Groups	95% Confidence Interval of the Difference				
	t	Df	Mean Difference	Upper	Lower
Group B	25.280	49	166.480	153.25	179.71
Group C	29.677	49	243.840	227.33	260.35
Group D	34.779	49	408.000	384.42	431.58

Group B showed a mean sensory blockade of 166.32± 46.6minutes, assessed using a pin prick test. The sensory block ranged from 84 minutes to 278 minutes. Group C showed a mean sensory blockade of 254.3± 50.18 minutes with sensory blockade ranging from 164 minutes to 389 minutes. Group D showed a sensory-motor blockade of 466.7± 83.6minutes, assessed using the pinprick method. The sensory block ranged from 259 minutes to 596 minutes.

Table No: 02- Comparison Of Mean Duration Of Sensory Block In Minutes Assessed Using Pinprick Test

Groups	95% Confidence Interval of the Difference				
	T	Df	Mean Difference	Lower	Upper
Group B	25.198	49	166.3200	153.055	179.584
Group C	34.769	49	458.5000	432.000	485.000
Group D	39.456	49	466.680	442.916	490.443

Of the three groups of patients, Group D showed the longest duration of mean sensory blockade followed by Group C whereas Group B had the least duration of mean sensory blockade. Moreover, the difference in duration of mean sensory blockade among the three groups of patients was statistically very highly

significant with unpaired student 't' test *i.e.,* "p" value less than 0.001. The mean heart rate of patients at the preoperative interval was 79.3 ± 2.5, 77.9 ± 4.4, and 77.8 ± 3.4 in patients of Group B, Group C, and Group D respectively. The mean heart rate of patients at the preoperative interval were showing significant intergroup differences (p=0.010). The mean heart rate of patients of Group B, was slightly higher than that of Group C and Group D. At spinal, a slight fall in the mean heart rate of patients in Group B, Group C, and Group D was observed and it reached to 76.5 ± 4.1bpm, 74.8 ± 4.0bpm and 74.2 ± 4.2bpm respectively, showing significant intergroup difference (p=0.019) with Mean heart rate of patients of Group B again slightly higher than that of Group C and Group D.At 3minutes and at subsequent intervals mean heart rate in Group B ranged from 79.0 ± 4.5bpm (at 3minutes) to 77.4 ± 5.1bpm (at 180minutes) whereas in Group C it ranged from 77.4 ± 6.1bpm (at 3minutes) to 76.0 ± 5.9bpm (at 180minutes) and Group D it ranged from 77.8 ± 3.4bpm (at 3minutes) to 79.0 ± 5.3bpm (at 180minutes). Systolic blood pressure of patients preoperatively was 128.5 ± 5.3, 127.4 ± 5.1, and 126.6 ± 5.7 in patients of Group B, Group C, and Group D respectively. The mean systolic blood pressure of Group B was slightly higher than Group C and Group D. At the time when spinal anesthesia was given, a slight fall in the Systolic Blood Pressure of patients in Group B, Group C, and Group D was observed and it reached to 125.9 ± 3.6mm Hg, 126.6 ± 3.2mm Hg and 125.6 ± 4.1mm Hg respectively, with the fact that the systolic blood pressure of Group C and Group D were slightly lower as compared with

the Group B. At 3 minutes and subsequent intervals, Systolic Blood Pressure in Group B ranged from 125.4 ± 5.8mm Hg (at 3 minutes) to 112.6 ± 4.6mm Hg (at 180minutes) whereas in Group C it ranged from 121.4 ± 4.6mm Hg (at 3minutes) to 118.6 ± 2.8mm Hg (at 180minutes) and Group D it ranged from 119.4 ± 3.6 mm Hg (at 3minutes) to 122.6 ± 3.0mm Hg (at 180minutes). Diastolic blood pressure of patients preoperatively was 82.9 ± 2.5, 80.9 ± 4.4, and 79.5 ± 4.3 in patients of Group B, Group C, and Group D respectively. The mean diastolic blood pressure of Group B was slightly higher than Group C and Group D.At the time when spinal anesthesia was given, a slight fall in the Diastolic Blood Pressure of patients in Group B, Group C, and Group D was observed and it reached to 81.0 ± 4.1mm Hg, 79.8 ± 4.0mm Hg and 7 7.6 ± 3.7mm Hg respectively, and the diastolic blood pressure of Group C and Group D was slightly lower as compared with the Group B. At 3 minutes and subsequent intervals, Diastolic Blood Pressure in Group B ranged from 81.1 ± 1.8mm Hg (at 3 minutes) to 70.0 ± 4.1mm Hg (at 180minutes) whereas in Group C it ranged from 80.5 ± 3.8mm Hg (at 3minutes) to 71.8 ± 4.0mm Hg (at 180minutes) and Group D it ranged from 80.2 ± 3.4mm Hg (at 3minutes) to 70.7 ± 4.6mm Hg (at 180minutes). Mean heart rate of patients preoperatively was 78.8 ± 3.2, 76.3 ± 3.3, and 76.1 ± 2.1 in patients of Group B, Group C, and Group D respectively, with Group C and Group D showing slightly lower mean heart rates as compared with that of the mean heart rate of Group B. The results were statistically significant.

Table No: 3-Comparison Of Post-Operative Heart Rate (Bpm) Between Three Groups At Different Time Intervals

S.No	Time Interval (hours)	Group B (n=50)			Group C (n=50)			Group D (n=50)			Significance of difference	
		N	Mean	SD	N	Mean	SD	N	Mean	SD	"t"	"p"
1	Immediate post-op	50	78.8	3.2	50	76.3	3.3	50	76.1	2.1	0.622	0.109

2	1	50	77.4	6.7	50	76.9	6.1	50	75.5	2.8	0.524	**0.019**
3	2	48	77.3	5.1	44	76.8	2.1	50	75.5	3.2	0.519	0.093
4	3	47	75.3	3.2	44	74.4	6.1	50	73.3	2.8	0.605	**0.024**
5	4	47	72.9	6.7	42	71.5	2.1	50	70.1	3.2	0.175	**0.031**
6	5	47	72.2	5.1	41	71.4	2.8	47	70.5	5.0	0.293	0.070
7	6	45	71.0	2.3	40	70.1	3.2	46	68.5	6.1	0.524	**0.001**
8	7	45	71.2	5.7	38	70.5	6.7	43	68.3	2.1	0.519	**0.005**
9	8	42	69.9	4.6	37	68.5	5.6	45	66.3	2.8	1.364	0.075

The mean systolic blood pressure of patients at the immediate post-operative interval was 126.1 ± 3.2, 123.8 ± 4.6, and 122.9 ± 5.2 in patients of Group B, Group C, and Group D respectively. Group C and Group D showed slightly lower mean systolic blood pressure as compared with the mean systolic blood pressure of Group B and the values were statistically significant. Mean diastolic blood pressure of patients at the immediate post-operative interval was 85.3 ± 1.6, 84.4 ± 3.8, and 81.0 ± 3.4 in patients of Group B, Group C, and Group D respectively, with Group C and Group D showing slightly lower mean diastolic blood pressure as compared with that of the mean diastolic blood pressure of Group B. Of the three groups of patients, Group D showed the longest duration of the meantime of rescue analgesia followed by Group C whereas Group B had the least duration of the meantime of rescue analgesia. Moreover, the difference in duration of the meantime of rescue analgesia among the three groups of patients was statistically very highly significant with unpaired student t-test *i.e.,* "p" value less than 0.001.

Table No: 4-Comparison Of Meantime For Rescue Analgesia In Minutes.

Groups	95% Confidence Interval of the Difference					
	T	Df	Mean Difference	Standard Deviation	Lower	Upper
Group B	27.6	49	235.6	24.6	189	307
Group C	31.2	49	346.8	43.1	287	415
Group D	34.7	49	484.9	19.8	390.8	539.8

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Of the three groups of patients, group D showed the least mean score on VAS followed by Group C whereas Group B had the largest mean VAS score. Moreover, the difference in duration of mean VAS score among the three groups of patients was statistically very highly significant with unpaired student t-test *i.e.,* "p" value less than 0.001. All three groups of patients did not show any significant changes in the hemodynamic status which required any intervention.

Discussion:

The mechanisms of the analgesic action of α_2-agonists have not been fully elucidated. The activation of inwardly rectifying G_1-protein-gated potassium channels results in membrane hyperpolarization decreasing the firing rate of excitable cells in the central nervous system (CNS). This is considered a significant mechanism of inhibitory neuronal action of α_2-adrenoceptor agonists. [8] Another prominent physiologic action ascribed to α_2-adrenoceptors is their reduction of calcium conductance into the cell, thus inhibiting neurotransmitter release[28]. These two mechanisms represent two very different ways of effecting analgesia: in the first, the nerve is prevented from ever firing, and in the second, it cannot propagate its signal to its neighbor. Activation of the receptors in the brain and spinal cord inhibits neuronal firing causing hypotension, bradycardia, sedation, and analgesia.[9] In general, presynaptic activation of the α_2-adrenoceptor inhibits the release of norepinephrine terminating the propagation of pain signals. Postsynaptic activation of α_2-adrenoceptors in the central nervous system inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Administration of an α_2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation. Most of the clinical experience gained in the use of intrathecal α_2-adrenoceptor agonists have been described with Clonidine.[10] The use of intrathecal Clonidine has a well-established synergetic effect with local anesthetics. Clonidine prolongs the duration of intrathecally administered local anesthetics and has potent antinociceptive properties.[11] Although such prolongation of the effects of local anesthetics has

been reported for oral and IV Clonidine administration, the intrathecal route is more effective in prolonging Bupivacaine spinal anesthesia. [12]In our study we compared the duration of sensory and motor block in the three groups of patients, Group B was given Intrathecal Bupivacaine alone, Group C was given intrathecal Bupivacaine plus Clonidine and group D was given intrathecal Bupivacaine plus Dexmedetomidine. As compared to group B, we found that the Group C patients had prolonged motor and sensory blockade (p less than 0.05). [13] These results were similar to the findings reported by Shukla D et al in their studies done on patients who underwent TURP and orthopedic surgeries respectively. In either of the groups, we did not observe any hypotension either during or after anesthesia. Further, even though there was statistically significant bradycardia (p = 0.03) it was not significant enough to warrant treatment with IV Atropine.[14]. This higher incidence of side effects may be attributed to the higher dose (150μg) of Clonidine received by the patients in these studies as compared to a lower amount (30μg) received by patients in our study. [15] Rhee K et al have substantiated the fact that higher incidence of side effects such as hypotension and bradycardia increase with the increase in the dose of Clonidine (more than 100μg). Fewer studies are available that compare a combination of intrathecal Dexmedetomidine and local anesthetics. Fukushima et al administered 2μg/kg epidural Dexmedetomidine for postoperative analgesia in humans but did not report neurologic deficits. In our study, the patients administered 5μg Dexmeditomedine reported the longest duration of sensory and motor block (mean 466.68 and 408.00minutes).[16].Of the three groups of patients, Group D showed the longest duration of meantime for rescue analgesia (484.90minutes) followed by Group C (346.80minutes) whereas the Group B required rescue analgesia earliest (235.6minutes). Among the groups of patients, Group D showed the least mean score on VAS (4.6) followed by Group C (5.3) whereas Group B had the highest mean VAS score (6.8). These findings are in conformity with the reported pattern of observations in other similar studies.[17,18]

Conclusion: Dexmedetomidine a newer Alpha 2-agonist seems to be an attractive adjuvant to spinal Bupivacaine even in doses as low as 5μg. Clonidine can be considered a good choice as an adjuvant if its

dose is kept at a lower-level range (less than $100\mu g$). However, Dexmeditomidine provides a longer duration of sensory and motor block and postoperative analgesia when compared with Clonidine. The incidence of side effects is low with both drugs if their doses are kept in the lower range. To conclude both of these combinations provide prolonged sensory and motor blockade, hemodynamic stability, Minimal side effects, and excellent intraoperative and postoperative analgesia.

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