EFFECT OF INTRAVENOUS DEXMEDITOMEDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA IN PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES: A RANDOMISED DOUBLE BLIND CLINICAL TRIAL

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ABSTRACT: BACKGROUND: In the present day practice of anaesthesia, bupivacaine is the most commonly used drug for spinal anaesthesia. To improve the quality of analgesia and prolong the duration of anaesthesia many adjuvants have been used namely Neostigmine, Clonidine, Propofol. The new α_2 agonist dexmedetomidine has been proved to prolong the spinal anaesthesia. We hypothesized that dexmedetomidine when administered intravenously as an adjuvant to spinal anaesthesia prolongs spinal analgesia. **METHODS:** 90 patients of ASA grade I & II were randomly allocated into two equal groups namely Group A and Group B. Group A received 3.5ml of 0.5% hyperbaric bupivacaine. Group B received 3.5ml of 0.5% hyperbaric bupivacaine followed by loading dose of 1 μ g/kg of dexmedetomidine intravenously 30mins after the subarachnoid block and maintenance infusion dose of 0.5 μ g/kg/hr till the end of surgery. Patient in Group A received normal saline. The regression to reach S1 sensory level and Bromage 0 (zero) motor scale, haemodynamic changes and level of sedation were recorded. **RESULTS:** The duration of sensory block was 246.33 $\pm$ 51.41 min in Group B as compared to Group A (176.89 $\pm$ 34.22). The duration of sensory block was longer in Group B. The duration of motor blockade was longer in Group B than Group A (193.33 $\pm$ 34.24 Vs 159.78 $\pm$ 23.52). Bradycardia and hypotension was more in Group B than Group A but was not significant

KEYWORDS: Spinal anaesthesia, Bupivacaine, Dexmedetomidine.

INTRODUCTION: Spinal anaesthesia is a widely used regional anaesthetic technique for lower abdominal surgeries¹. Hyperbaric 0.5% bupivacaine is the common drug used for surgeries lasting for 2-3 hours. Despite many advantages of spinal anaesthesia, the relatively short duration of the local anaesthetic drug during prolonged surgery can be a problem. Prolonging duration of spinal anaesthesia would provide more time for surgical intervention. Various additives like epinephrine, magnesium sulfate and α_2 agonist have been used in order to prolong the duration of spinal anaesthesia.

α_2 receptor agonists are being increasingly used in critical care and anaesthesia. Beside sedation and analgesia, they also decrease sympathetic tone and attenuate the stress responses to surgery. Dexmedetomidine was approved by FDI in 1999 for use in humans for analgesia and sedation in intensive care.² Memis and coworkers were the first clinician who demonstrated that adding 0.5 μ g/kg dexmedetomidine to lignocaine improves the quality of anaesthesia and post-operative analgesia.³ IV Dexmedetomidine has been found to reduce the inhalational anaesthetic requirement during general anaesthesia.⁴

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However literature pertaining to the effects of intravenously administered dexmedetomidine on spinal anaesthesia is sparse. So the purpose of this study was to compare the duration of sensory and motor block, as well as hemodynamic changes and level of sedation following intrathecal bupivacaine versus intrathecal bupivacaine supplemented with a low dose of IV dexmedetomidine.

METHODS AND MATERIALS: A randomized, double blind, prospective study was conducted on 90 patients of American Society of Anesthesiologist Grade I & II, aged between 20 and 60 years of either sexes undergoing lower abdominal surgery.

After obtaining institutional ethical approval and informed consent, patients were randomly allocated into 2 groups, Group A (control) and Group B (Study Group) using computer generated random numbers. Patients of American Society of Anesthesiologist Grade III & IV, Body mass Index more than 25kg/m², Height less than 150cms, Patients using α_2 receptor antagonists, infection at the puncture site, coagulopathy, having hypersensitivity to drugs were excluded from the study.

All patients were advised nil per oral for 8 hrs and pre-medicated the previous night of surgery with Tab. Rantac 150mg and Tab. Alprazolam 0.5mg. In the operation theatre, all patients were connected to electrocardiography, peripheral oxygen saturation (SPO₂) and non-invasive blood pressure monitor and all the basal parameters were recorded. An Intravenous line was obtained with 18Gauge cannula and all patients were preloaded with Ringer lactate solution 10ml/kg body weight 15 minutes before the surgery.

With the patient in sitting position, spinal anaesthesia was performed at the level of L₃ – L₄ through a midline approach using a 25G Quincke spinal needle. Bupivacaine 0.5% (H) was injected at a rate of 0.2ml/seconds. Patients were randomly allocated into two groups. Group A received 3.5ml of 0.5% hyperbaric bupivacaine followed by isotonic saline intravenous infusion. Group B received 3.5 ml of 0.5% hyperbaric bupivacaine followed by loading dose of 1µg/kg of intravenous dexmedetomidine with normal saline in a concentration of 4µg/ml. 50cc syringe was prepared with either normal saline or dexmedetomidine diluted with normal saline in a concentration of 4µg/ml.

Immediately after spinal anaesthesia patients were laid back to supine position. Patients allocated to Group B received intravenously through the intravenous infusion pump a loading dose of 1µg/kg dexmedetomidine over 10mins and a maintenance dose of 0.5µg/kg/hr till the end of the surgery. Patients in Group A received also in 10mins, the same volume of normal saline as loading dose and maintenance dose as in Group B.

The intravenous medication was prepared by an anesthesiologist and was passed on to an anesthesiologist who performed the spinal anaesthesia who was blinded as to which group the patients were allocated. The anesthesiologist to perform the block recorded the baseline value of vital signs (blood pressure, heart rate and peripheral O₂ saturation every 5 minutes till the end of the surgery. Sensory blockade was assessed using pinprick in the midclavicular line bilaterally.

Total duration of sensory block was recorded. Recovery time for sensory blockade was the time taken to reach S₁ dermatome. The motor blockade was determined using Bromage scale⁵. (0: no paralysis); 1= unable to raise extended leg; 2= unable to flex knee; 3= unable to flex ankle.

SEDATION: The Ramsay sedation score was used to assess the level of sedation; intra-operatively and post operatively every 15 mins.⁶

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ANALGESIA: The Visual Analog Scale was used to assess the level of pain. Cut off point to treat pain was ≥ 4 on the visual analog scale. Rescue analgesia consisted of intravenous infusion of Diclofenac sodium 75mg mixed in 100ml of DNS at a rate of 100ml/hr.

Hypotension was defined as $> 20\%$ fall of baseline blood pressure and was treated with rapid infusion of intravenous fluid and bolus dose of 6mg of intravenous ephedrine. Respiratory depression defined as Spo_2 less than 90% Spo_2 on room air and was treated with oxygen face mask and respiratory support if required.

Total duration of analgesia was defined as time from administration of SAB until the first complaint of pain ($\text{VAS} \geq 4$). Complications such as hypotension, bradycardia, nausea, vomiting, shivering, urinary retention and headache were noted and treated accordingly. An Anesthesiologist, who was blinded to the study drug, documented all the parameters.

STATISTICAL ANALYSIS: Purposive random sampling method was employed to arrive at the sample size. The statistical analysis was carried out in Microsoft office Excel 2007.

The observations are expressed as mean $\pm$ one standard deviation. The baseline, intra operative and post – operative hemodynamic changes at various time intervals were compared using unpaired 't' test and chi-square test. The values of $P < 0.05$ were statistically significant. The adverse events and treatment are expressed as percentage.

RESULTS: Ninety patients ($A=45$) and $B=45$ were enrolled, completed the study protocol and were included in the data analysis. The demographic data did not differ between the two groups (Table 1)

The mean duration of sensory blockade (i.e. regression to S_1 dermatome) and motor blockade (Bromage Scale 0) was significantly prolonged in group B in comparison with group A. The mean duration of sensory blockade in group A was 176.89 ± 34.22 min and group B 246.33 ± 51.44 min, the P value < 0.001 . The mean duration of motor blockade was 159.78 ± 23.52 min in group A and 193.33 ± 34.24 min in Group B. The difference was statistically significant ($P < 0.001$). (Table 2) (fig. 1) The time for first rescue analgesia was 202.89 ± 46.58 min in Group A and 303.67 ± 39.75 min Group B. This was statistically significant. Pain score were measured using visual analog scale in PACU and they were statistically significant. (Table 3) (Fig. 2).

Baseline hemodynamic, intra-operative hemodynamic and post-operative haemodynamics (i.e. Heart rate, Blood pressure and Spo_2) was compared between two groups. The data did not differ between the two study groups (fig. 3).

Ramsay sedation scale ranged between 1-2 in group A and 2 to 2.35 in group B. The sedation score was significantly higher in Group B ($P < 0.05$) (Table 4) (figure 4).

Nausea/ vomiting, Bradycardia, Hypotension, Respiratory depression, Shivering, need for Atropine, need for Ephedrine were comparable in the two groups ($P > 0.05$). In Group A, 2% of patients had vomiting compared to 0% in Group B. In Group A, bradycardia was observed in 8% of patients as compared to 20% IN Group B. Bradycardia was treated with Inj. Atropine 0.6mg intravenously. In Group A, hypotension was observed in 8% of patients as compared to 28% of patients in Group B. Hypotension was observed 20 minutes following the start of dexmedetomidine infusion and was treated with Inj. Ephedrine 6mg intravenously bolus (Table 5)

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Parameter	Group A	Group B	p value
Age (Years)	45.44±7.60	46.20±8.36	0.658
BMI (kg/m ²)	20.44±1.82	19.98±2.01	0.269
Sex(Male/Female)	14:31	13:32	-

Table 1: Demographic data

Age and BMI are expressed as Mean±Standard deviation

Parameter	Group A (Mean±SD)	Group B (Mean±SD)	p value
Sensory (min)	176.89±34.22	246.33±51.41	<0.001
Motor (min)	159.78±23.52	193.33±34.24	<0.001

Table 2: Duration of Sensory and Motor Blockade

VAS	Group A(Mean)	Group B(Mean)	p value
Postoperatively (min)			
0	2.13	0.71	<0.001
15	2.35	0.84	<0.001
30	2.46	1.35	<0.001
45	3.08	1.55	<0.001
60	3.80	1.93	<0.001
75	4.35	2.33	<0.001
90	4.93	2.97	<0.0010

Table 3: VAS Scores

Parameter	Group A (Mean±SD)	Group B (Mean±SD)	p value
Heart rate (HR)	76.84±8.92	78.88±8.68	0.279
Systolic BP (SBP)	114.29±8.60	113.58±10.94	0.735
Diastolic BP (DSP)	73.31±6.63	72.51±7.06	0.585
Mean Arterial Pressure (MAP)	86.88±7.84	85.62±7.01	0.426
SPO ₂	99.56±0.20	99.86±0.49	0.279

Table 4: Intra-operative hemodynamic

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Sedation Score	Group A (Mean)	Group B (Mean)	p value
Postoperatively(min)			
0	2	2.24	0.04
15	1.95	2.33	0.006
30	1.82	2.35	0.0001
45	1.82	2.24	0.003
60	1.48	2.13	0.0001
75	1.02	2.15	0.0001
90	1	2.11	0.0001

Table 5: Sedation Score

Adverse effects	Group A	Group B
Nausea/Vomiting	1(2%)	0(0%)
Bradycardia	9(20%)	4(8%)
Hypotension	13(28%)	4(8%)
Respiratory depression	0(0%)	0(0%)
Shivering	1(2%)	0(0%)
Atropine	9(20%)	4(8%)
Ephedrine	13(28%)	4(8%)
Inadequate block	2(4%)	0(0%)

Table 6: Adverse events and treatment

Fig. 1: Motor and sensory blockade

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Fig. 2: Visual Analog Scale

Fig. 3: Intra-operative hemodynamic

Fig. 4: Ramsay sedation Scores

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DISCUSSION: Dexmedetomidine has become the frequently used drug in anaesthetic armamentarium along with routine anaesthetic drugs, due to its hemodynamic, sedative, anxiolytic, analgesic, neuroprotective and anaesthetic sparing effects.

α_1 to α_2 ratio of 1:1600 makes it a highly selective α_2 agonist compared to clonidine, thus reducing the unwanted side effects involving α_1 receptors.⁷ Dexmedetomidine is pharmacologically related to clonidine, has 8 times more affinity for α_2 receptors than clonidine. It produces sedation and anxiolysis by binding to α_2 receptors in the locus ceruleus, which diminishes the release of norepinephrine and inhibits sympathetic activity, thus decreasing heart rate and blood pressure. It produces analgesia by binding to adrenoreceptors in the spinal cord.⁸

This prospective randomized study demonstrated that peri-operative administration of dexmedetomidine prolongs duration of sensory blockade, motor blockade. It also increases the time for first rescue analgesia.

The dexmedetomidine infusion results in increased activation of α_2 receptors at the spinal cord and resulting in inhibition of nociceptive impulse transmission.⁹

In our study dexmedetomidine was used both as a loading dose followed by infusion. It demonstrated prolongation of the duration of sensory and motor blockade. Lugo et al¹⁰ in their study demonstrated the prolongation of sensory block and duration of analgesia without significant effect on motor block. They used 1mcg/kg of dexmedetomidine as loading dose followed by infusion of 0.5mcg/kg/hr. Abdalah et al¹¹ in their study concluded that I.V dexmedetomidine can prolong the duration of sensory block, motor block and increased time for first analgesic request associated with spinal anaesthesia.

Al Mustafa et al¹² demonstrated that supplementation of spinal anaesthesia with intravenous dexmedetomidine produces significantly longer sensory and motor block than spinal anaesthesia alone. S.S Harsoor et al¹³ in their study found that administration of I.V dexmedetomidine during spinal anaesthesia hastens the onset of sensory block and prolongs that duration of sensory and motor block with arousable sedation even at loading dose of 0.5 μ g/kg. In our study we used 1 mcg/kg. of loading dose of dexmedetomidine followed by infusion of 0.5 μ g/kg/min and our results were comparable with the above studies.

In our study, motor block was prolonged. However in a study conducted by Kayer et al¹⁴ use of single dose of 0.5 μ g/kg of dexmedetomidine did not affect the duration of motor block. The prolongation of motor block observed in our study may be attributed to the continuous infusion following the loading dose. The mechanism of motor block is unclear; the analgesic effects of α_2 agonist could be mediated through supraspinal, spinal and peripheral actions.²

There was minimal decrease in heart rate and blood pressure in patients receiving dexmedetomidine in our study, similar to observation of other authors.¹² Dexmedetomidine does not appear to have any direct effects on heart¹⁵. The hypotensive and bradycardia effects of dexmedetomidine is caused by inhibition of the central sympathetic outflow.¹⁶ The other possible explanation for decrease hemodynamic parameters is the stimulation of the pre-synaptic α_2 -adrenoreceptor, leading to decreased norepinephrine release.¹⁷

Dexmedetomidine is known to have sedative effect, providing better conditions for surgeons and patients provided that hemodynamic stability is preserved.¹⁸ Intra-operative sedation provided by dexmedetomidine eliminates the need for additional sedatives. Dexmedetomidine produces sedation by its central effects and seem to be dose dependent.¹⁹

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In our patients Ramsay Sedation Scores ranged from 2-2.35. Most of the patients receiving dexmedetomidine were sedated but easily aroused in our study. Kaya et al¹⁴ also had similar observations regarding sedation in their study.

Respiratory rate was lower in patient receiving dexmedetomidine, but clinically not significant and oxygen saturation was maintained equally in both the groups. Harsoor et al¹³ observed similar results in their study.

CONCLUSION: Intravenous dexmedetomidine administration prolonged sensory and motor blockade of intrathecal 0.5% hyperbaric bupivacaine with good hemodynamic stability and arousable sedation.

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