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ORIGINAL ARTICLE

INTRAVENOUS DEXMEDETOMIDINE PROLONGS BUPIVACAINE SPINAL ANESTHESIA

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ABSTRACT: BACKGROUND: Dexmedetomidine is a potent selective alpha 2 agonist, which may prolong bupivacaine spinal block providing good cooperative sedation and longer post-operative analgesia. **AIMS:** This study aims at evaluating the efficacy of Intravenous dexmedetomidine over intravenous midazolam during intrathecal 0.5% bupivacaine in hysterectomy patients. **METHODS:** In a randomized prospective double blinded study, 50 ASA I patients posted for hysterectomy were recruited and divided in two groups: Group D received dexmedetomidine infusion 0.5 mcg/kg/hr. 5 minutes after spinal block with 0.5% bupivacaine 3ml, and Group M received midazolam infusion 0.04 mg/kg/hr. after 5 minutes of spinal block with 0.5% bupivacaine 3 ml. The maximum upper level of sensory block, time for regression of sensory and motor blocks was recorded. Post-operative analgesic requirements and sedation were observed. **RESULTS:** T6 was the highest level of sensory block in 72 % patients in dexmedetomidine group while in midazolam group only 28 % patients attained T6 level ($p<0.001$). Time for two segment regression of sensory block was longer in dexmedetomidine group, than in midazolam group ($p<0.001$). The motor block duration was similar in both the groups. The highest VAS pain score was lower in dexmedetomidine group ($p<0.001$). The time for first rescue analgesia was longer in dexmedetomine group ($p<0.001$). **CONCLUSION:** Intravenous dexmedetomidine is the better adjuvant in patients under spinal anesthesia. In addition to a cooperative sedation, a higher and a longer sensory block, and a longer pain free post-operative period was obtained.

KEYWORDS: Spinal anesthesia, Cooperative sedation, post-operative analgesia.

INTRODUCTION: Central neuraxial blockade is a widely used anesthetic procedure. Intra-operatively the patients remain awake and anxious thereby requiring the use of sedatives. Benzodiazepines, Propofol and narcotics are used for their sedative and analgesic properties. But they are associated with cardiorespiratory depression.[1-4] Intravenous midazolam, which is used most often in this situation, has sedative action, but doesn't have analgesic effect.

Dexmedetomidine is an α2 adrenergic agonist[5] with sedative, anesthetic sparing and analgesic properties, with lack of respiratory depression.

Our study was based on evaluating the efficacy of dexmedetomidine over midazolam in providing sedation during spinal anesthesia using 0.5% bupivacaine. We also looked into the cardio-respiratory variables, the effects on sensory and motor blocks, sedation, analgesia, and any adverse effects.

METHODS: After the approval of the institutional ethical committee, a randomized prospective double blinded study was planned. This study was done over a period of 6 months from March 2010 to Sep 2010. Patients included were of ASA physical status 1 or 2 aged 18-65 years posted for elective

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hysterectomy. All were to be given spinal anesthesia with 0.5 % bupivacaine 15 mg. Exclusion criteria included use of any opioid or sedative medication in the week prior to surgery, history of alcohol/ drug abuse, heart dysfunction, morbidly obese, on anti-hypertensive therapy or contraindication to spinal anesthesia. Patients with diabetes and renal dysfunction were excluded. Patients were randomized to one of the two groups by "sealed envelope" method:

Group D (n=25) receive sedation with dexmedetomidine infusion 0.5mcg/kg/hr.

Group M (n=25) receive sedation with midazolam infusion 0.04mg/kg/hr.

Informed consent of the patients was taken.

On the day of surgery patients did not receive any premedication. They were preloaded with lactated ringer's solution at 15ml/kg through an 18 gauge cannula. All patients were monitored with electrocardiogram, pulse oximetry and automated non-invasive blood pressure. Spinal anesthesia was administered with sterile disposable 25 gauge Quincke needle using 0.5% bupivacaine 15 mg in L3-4 interspace in sitting position under aseptic precautions. Patients were immediately positioned supine and sensory blockade level (pin prick) was tested 1 minute later and then every 5 minutes. Dexmedetomidine/ midazolam infusions were started 5 minutes after the intra thecal injection. Sensory and motor blocks were assessed every two minutes for the first ten minutes. The maximum upper level of sensory blockade was noted. Motor block (Modified Bromage) was evaluated until total motor block. Oxygen was delivered by face mask at 5L/mt throughout the surgery. Drug infusion was discontinued if any of the following adverse effects was observed – apnea > 20 seconds, SpO2 < 90%, heart rate < 50 beats/ minute, systolic blood pressure < 30% initial level. The infusion was stopped after skin suturing. Sedation was evaluated on a 6 point Ramsay Sedation score (RSS) .Analgesia was assessed by Visual analog scale (VAS), VAS; 0= no pain; 10= worst possible pain at 4, 8, 12 and 24 hours. If VAS > 6, 50 mcg then IV fentanyl was given.

The following parameters were measured every 5 minutes intraoperatively; heart rate (HR), systolic blood pressure (SBP), respiratory rate (RR), and oxygen saturation (SpO2). The operative time did not exceed 90 minutes. RSS and VAS were assessed post operatively in the PACU. VAS was assessed until RSS reached score 4.

Hypotension was defined as a fall in systolic blood pressure > 30% baseline or < 80 mm Hg and was treated with incremental IV doses of ephedrine 5 mg or bolus crystalloids if required. Bradycardia was defined as heart rate < 50 beats per minute and was corrected with IV atropine 0.6 mg.

Patients were shifted to their wards when RSS was 2 point. The duration of sensory and motor block was assessed. The persistence of sensory anesthesia was taken as the time required for the upper level of sensory block to regress 2 dermatomes. Motor block duration was taken as the time elapsed before the patients were able to bend the knee but unable to raise the leg (modified Bromage score=1). A 24 hour follow up was done to assess the analgesic requirement. The time taken for the first demand of post-operative analgesic was recorded.

Descriptive statistical analysis has been carried out in this study. Student t test was used to find the significance of study parameters on continuous scale between 2 groups on metric parameters. Chi square test has been used to find the significance of study parameters on categorical scale between 2 or more groups. P value 0.05 <p <0.1+suggests significant, 0.01 <p ≤0.05 * moderately significant, p ≤ 0.01 ** strongly significant. The statistical software namely SAS 9.2, SPSS

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15, Stata 10.1, Med Calc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of the data.

RESULTS: The study groups were comparable regarding age, ASA physical status, baseline systolic pressure and the duration of hysterectomy.

Variables	Group D	Group M	P value
Age (years)	44.40±8.07	43.32±6.99	0.616
Height (cm)	162.20±4.33	161.04±3.10	0.282
Weight (kg)	62.64±3.71	61.20±3.54	0.166
ASA I:II	60:40	60:40	
Duration of Surgery (minutes)	83.44±4.60	82.32±3.82	0.354

Table 1: Patient characteristics and duration of surgery

The baseline heart rate and systolic blood pressure were comparable in both the groups. After 10 minutes, that is 5 minutes of dexmedetomidine infusion the heart rate in group D was 58.68±5.12 bpm while in group M, it was 68.52±6.54 (p <o.oo1)[Table 2]. The reduction in heart rate was more in group D than in group M. 1 patient in group D had bradycardia that was corrected with 0.6 mg IV atropine.

HR (bpm)	Group D	Group M	P value
Baseline	100.72±11.14	98.44±8.19	0.414
At the time of spinal	98.80±13.26	98.40±6.33	0.892
2 minutes	92.44±12.00	91.04±5.45	0.598
4 minutes	80.48±8.37	78.76±4.75	0.376
6 minutes	77.88±7.88	75.84±3.51	0.192
8 minutes	73.28±6.48	70.24±4.14	0.101
10 minutes	58.68±5.12	68.52±6.54	<0.001**
20 minutes	56.72±4.59	73.28±6.83	<0.001**
40 minutes	60.76±7.82	78.72±5.19	<0.001**
60 minutes	76.28±5.33	79.60±5.63	0.037*
80 minutes	77.44±4.87	80.96±4.80	0.013*
100 minutes	78.84±4.76	81.83±6.24	0.064+

Table 2: Comparison of heart rate [HR] changes in the two groups

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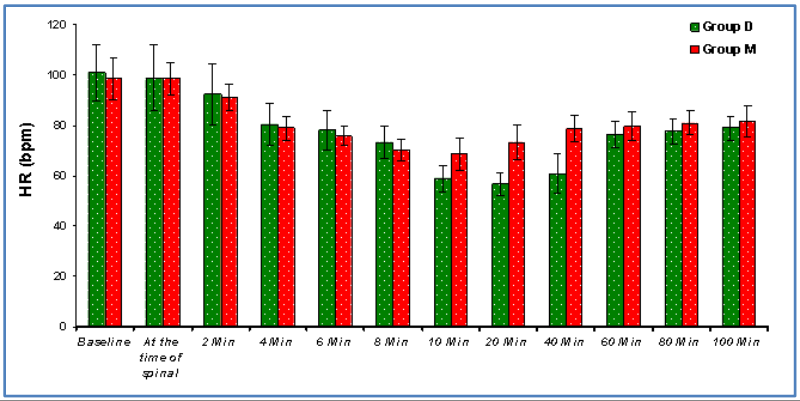

Fig. 1: Comparison of heart rate changes in the two groups

Group D recorded a significant fall in systolic blood pressure (SBP) after 40 minutes ($p < 0.006$) [Table -3]. The fall was for 20 minutes [figure 2]. 1 patient developed hypotension requiring ephedrine correction.

SBP (mm Hg)	Group D	Group M	P value
Baseline	131.72±8.23	135.44±9.98	0.157
At the time of spinal	135.92±4.74	138.44±7.33	0.156
2 minutes	128.52±12.12	133.32±9.13	0.120
4 minutes	119.64±9.45	123.08±8.70	0.187
6 minutes	112.36±9.45	116.16±6.39	0.102
8 minutes	110.08±8.33	113.12±6.88	0.166
10 minutes	111.52±6.8	113.36±9.57	0.437
20 minutes	113.28±5.53	117.04±10.80	0.128
40 minutes	117.52±7.22	123.68±7.85	0.006**
60 minutes	118.56±5.87	125.68±5.38	<0.001**
80 minutes	120.48±7.35	126.40±4.80	0.001**
100 minutes	123.68±6.05	128.24±6.62	0.014*

Table 3: Comparison of systolic blood pressures [SBP] in the two groups

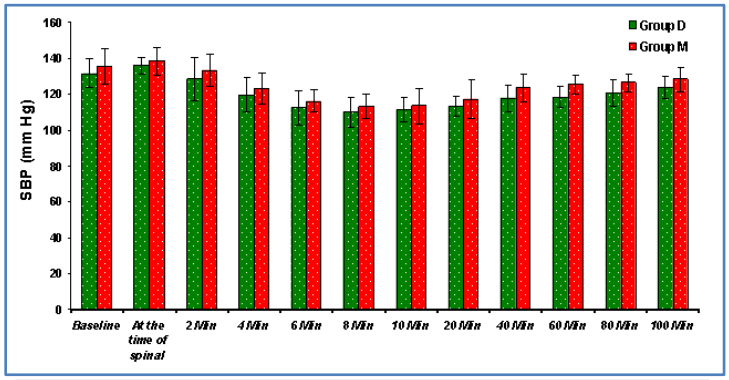

Fig. 2: Hemodynamic changes in the two groups

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Group D has recorded a higher level of sensory block. [Table-4]. T6 was the highest sensory level in 72% patients in group D while only 28 % had the same in group M (p<0.001).

Highest sensory level	Group D (n=25)	Group M (n=25)	P value
T6	18(72.0%)	7(28.0%)	<0.001**
T7	5(20.0%)	6(24.0%)	0.7333
T8	2(8.0%)	12(48.0%)	0.002**
Inference	Sensory level of (T5-7) is significantly associated with Group D with P=0.004**		

Table 4: Comparison of highest sensory level in the two groups

The time for 2 segment regression of sensory block was longer in Group D. [Table 5]. In group D it was 206.40±21.87 minutes and in group M it was 163.64±20.85 minutes (p <0.001). The time for motor block to come to Modified Bromage 1 was similar in the two groups (p=0.103). The sedation score was also not different in the two groups (p=0.257). The highest VAS score in group D was 4.4±1.4, while in group M, it was 6.8±2.2 (p<0.001). The patients in group M had more pain. Group D patients had good analgesia; the demand for the first rescue analgesia was later (289.60±67.05 minutes) compared to group M (200.88±25.06 minutes). P value <0.001.

Outcome variables	Group D	Group M	P value
Time for 2 Segment Regression of Sensory Block	206.40±21.87	163.64±20.85	<0.001**
Time for Motor Block to Bromage1	238.08±34.16	230.040±18.37	0.103
Sedation Score	3.08±0.4	2.92±0.57	0.257
Highest Pain Score (VAS Score)	4.4±1.4	6.8±2.2	<0.001**
Time for 1st Rescue Analgesia	289.60±67.05	200.88±25.06	<0.001**

Table 5: Comparison of outcome variables in the two groups

One patient in group D had hypotension and bradycardia. Hypotension got corrected with 5 mg of ephedrine and bradycardia with 0.6 mg of atropine respectively. One patient had dry cough in Group D which subsided with saline nebulization. No patient in either group developed any respiratory depression.

Side effects	Group D (n=25)	Group M (n=25)
Bradycardia	1(4%)	0
Dry cough	1(4%)	0
Hypotension	1(4%)	0

Table 6: Comparison of side effects in the two groups

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DISCUSSION: Dexmedetomidine is an attractive alternative to anesthetic adjuvant used at present due to its anesthetic sparing and hemodynamic stabilizing effects[6-8]. Used along with regional anesthesia, dexmedetomidine prolongs the action of local anesthetics along with providing analgesia and sedation without causing respiratory depression[9]. Dexmedetomidine is also used as a sedative for monitored anesthesia care due to its analgesic properties, co-operative sedation and lack of respiratory depression[10-11] Like clonidine, dexmedetomidine enhances the effects of local anesthetics without any adverse effects.[12]

Memis et al[13] reported that addition of 0.5 mcg/kg dexmedetomidine to lidocaine for intravenous regional anesthesia shortened sensory and motor block onset times and prolonged their recovery times without any adverse effects. Coskuner et al[14] reported that intravenous dexmedetomidine enhanced the sensory block during epidural block with bupivacaine. Kaya et al[9] showed that dexmedetomidine premedication in bupivacaine spinal anesthesia gave a higher level sensory block than with midazolam.

This study showed that in comparison to midazolam infusion, a continuous dexmedetomine infusion at 0.5 mcg/kg/hr. following spinal anesthesia with 0.5% bupivacaine 3 ml, achieved a higher level of sensory block along with prolonging its duration. At the same time, there was good analgesia. The time for the demand of first rescue analgesia was increased. Sedation was comparable to midazolam. However bradycardia and hypotension was encountered which were easily corrected.

In our study T 6 was the upper level of sensory block in group D while in group M it was T 8. The time for two segment regression of sensory block was higher in group D ($p < 0.001$). The time for motor block to modified bromage 1 was similar in both. ($p = 0.103$).

The higher and a longer sensory block by intravenous dexmedetomidine may be due to its supraspinal, direct analgesic and/ or vasoconstrictive action. The conduction of sensory nerve fibers may be more inhibited than the motor nerve fibers as with clonidine[15]. The effect of dexmedetomidine is not dependent on the route of administration. But midazolam has anti-nociceptive property through neuraxial pathway. Its analgesic effect appears only after spinal or epidural route but not after intravenous administration.[16-18] In our study too, group D reported a lower VAS score than group M. Also the time to first rescue analgesia was longer in group D. The use of VAS score strongly points our hypothesis that dexmedetomidine lessens post-operative pain.

The sedation of dexmedetomidine differs from other sedatives in that the patient is easily arousable and is co operative[19]. Midazolam may however cause a paradoxical reaction[20]. The patient may be restless and disinhibited. In our study sedation was good in both groups.

Rapid or bolus administration of intravenous dexmedetomidine may cause transient rise in blood pressure and a reflex bradycardia[8]. We encountered hypotension and bradycardia in only one patient in group D. hypotension responded well to 5 mg ephedrine iv and bradycardia. This study was done on healthy young patients and we administered a fixed slow dexmedetomidine infusion with adequate hydration. Further studies are required to investigate the efficacy of dexmedetomidine in geriatric and medically compromised patients.

Gomez et al[21] concluded that dexmedetomidine provided good analgesia but was associated with hypotension and bradycardia. Alhashemi JA et al[22] found that dexmedetomidine was an effective sedative with better patient satisfaction, less opioid requirement and less respiratory depression than midazolam for MAC in cataract surgeries. Midazolam is known to cause apnea and arterial desaturation in sedative doses.[23]

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One limitation of this study is that since a fixed dose of both drugs was given we cannot comment on the effect on respiration. We have not encountered any change in respiratory parameters (respiratory rate, SpO_2).

CONCLUSION: Intravenous Infusion dexmedetomidine at 0.5mcg/kg/hour given along with intrathecal bupivacaine 0.5% 3ml in hysterectomy patients resulted in a sensory block which was higher as well as more prolonged than with infusion midazolam. Also a good quality of cooperative sedation was achieved. A good post-operative analgesia and a longer pain free interval reduced the post-operative opioid requirements. No respiratory depression was encountered. Bradycardia and hypotension may however occur, but are easily correctable.

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