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Comparative Study of Intravenous Dexmedetomidine (0.5 Microgram/ Kg) *Vs* Intravenous Midazolam (0.05 Mg/Kg) as Premedicant in Spinal Anesthesia with 0.5% Bupivacaine for Gynecological Surgeries

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Abstract

Introduction: Surgeries like direct and indirect inguinal hernia repair, lower limb surgeries, urological surgeries and gynecological surgeries are commonly done under spinal anesthesia. It is a selective α_2-adrenoceptor agonist and is currently used for its sedative, analgesic and sympatholytic properties. Intravenous Dexmedetomidine decreases the inhalational anesthesia and opioid requirements during general anesthesia**.** *Aims:* To compare the postoperative effect of intravenous dexmedetomidine in comparison with intravenous midazolam on intrathecal bupivacaine in patients undergoing gynecological surgeries under spinal anesthesia. *Materials and Methods:* Prospective randomized study between March 2017 and August 2018. This study was conducted in 100 patients belonging American Society of Anesthesiologists (ASA) physical status classification class 1 & 2 and undergoing gynecological surgeries under spinal anesthesia were included. *Results:* Postoperative analgesia was significantly prolonged with the use of intravenous dexmedetomidine premedication than with intravenous midazolam. Heart rates were lesser in dexmedetomidine Group A when compared to midazolam Group B, but overall requirement of anticholinergics was similar in both groups. Mean arterial pressures were lower with dexmedetomidine Group A when compared with midazolam Group B. *Conclusion:* Intravenous dexmedetomidine premedication prolongs the duration of sensory and motor blockade during the spinal anesthesia with Bupivacaine with good sedation and postoperative analgesia than with intravenous midazolam premedication in patients undergoing gynecological surgeries under spinal anesthesia.

Keywords: Dexmedetomidine; Midazolam; Bupivacaine; Premedication, Spinal anesthesia.

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Introduction

Surgeries like direct and indirect inguinal hernia repair, lower limb surgeries, urological surgeries and gynecological surgeries are commonly done under spinal anesthesia. Different adjuvants are used in spinal anesthesia along with intrathecal bupivacaine, with the possible advantages of prolonged action, reduced postoperative pain and lesser analgesic requirement postoperatively. Dexmedetomidine, an α_2-agonist, has been used for premedication and as an adjunct to general anesthesia. It is a selective

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α_2-adrenoceptor agonist and is currently used for its sedative, analgesic and sympatholytic properties 4. Intravenous Dexmedetomidine decreases the inhalational anesthesia and opioid requirements during general anesthesia.[1] Also, it has been used safely as premedication agent in patients undergoing surgical procedures under different regional anesthesia techniques. Dexmedetomidine has an inhibitory effect on the locus ceruleus (A6 group) located at the brain stem 6. This supraspinal action could explain the prolongation of spinal anesthesia after intravenous administration of Dexmedetomidine. Part of the mechanism by which Dexmedetomidine produces an antinociceptive effect is by acting directly on the locus ceruleus.[2] There is a growing interest in the use of α_2-adrenoceptor agonists as sedatives because of their favorable properties which include their relatively short half-life, analgesic effects, cardiorespiratory stability and rapid reversal of sedation on discontinuation of drug.[3]

Although a synergistic interaction between intrathecal Dexmedetomidine and local anesthetics has been observed in previous studies, there are few clinical studies with sample size of 25 per group regarding the effect of intravenous Dexmedetomidine premedication on the duration of sensory and motor block during spinal anesthesia.

This clinical study is to assess the effects of intravenous Dexmedetomidine premedication on spinal block duration and postoperative analgesia in patients undergoing surgeries under spinal anesthesia. To isolate dexmedetomidine's analgesic effects from its sedative effects, a comparison will be made with a benzodiazepine i.e., midazolam given by intravenous route to provide sedation. In this study, dexmedetomidine will be administered by intravenous route over 10 min., as rapid administration of dexmedetomidine may cause tachycardia, bradycardia, hypertension or hypotension. Hence, in this study 0.5 micrograms/kg. Dexmedetomidine is administered intravenously. Midazolam 0.05 milligram/kg. administered intravenously gives enough sedation and amnesia without any adverse effects on hemodynamics and respiration in patients undergoing surgeries under spinal anesthesia. Therefore, midazolam 0.05 milligram/kg. is administered intravenously to the patients in this study.

Materials and Methods

Prospective randomized study done as Hospital based, between March 2017 and August 2018. This study was conducted in Modern Maternity Hospital, Hyderabad, Telangana. 100 patients belonging American Society of Anesthesiologists (ASA) physical status classification class 1 & 2 and undergoing gynecological surgeries under spinal anesthesia were included. Using a computer-generated randomization schedule, the patients were randomly divided into two groups:

Group A: The first group are of 50 patients who were administered intravenous Dexmedetomidine 0.5 micrograms/kg. 15 minutes prior to spinal anesthesia with intrathecal bupivacaine 0.5% 3 ml. (n = 50).

Group B: The second group are of 50 patients who were administered intravenous midazolam 0.05 milligrams/kg. 15 minutes prior to spinal anesthesia with intrathecal bupivacaine 0.5% 3 ml (n = 50).

Inclusion Criteria

Healthy adult patients aged between 18 and 50 yrs. of either sex, Patients belonging to ASA class I/II.

Exclusion Criteria

Patients aged <18 years or > 50 years, ASA class III/IV, Use of any opioid or sedative medications in the week prior to surgery, History of alcohol or drug abuse, Known allergy to dexmedetomidine, midazolam or Bupivacaine, Contraindication to spinal anesthesia (e.g., coagulation defects, infection at puncture site, Preexisting neurological deficits in the lower extremities), Cardiovascular, Respiratory, Neurological, Endocrine, Hepatic, Renal disease or other comorbid conditions, Patients having inadequate subarachnoid blockade and who are later supplemented by General anesthesia, Patients with excessive blood loss and needing blood transfusion and Pregnant women.

This study was conducted under the guidance of senior anesthesiologist. All the emergency drugs and equipment were kept ready in the operating room. Patients were shifted to operation theatre and monitors connected. Monitors included Electrocardiography, Noninvasive blood pressure measurement and Pulseoximetry. The same monitor was used for all the patients in the study. After intravenous insertion of an 18-G catheter in the operating room, all patients received 20 ml/kg of lactated Ringer's solution intravascular volume loading before spinal anesthesia. Each group was premedicated with Dexmedetomidine and Midazolam 15 minutes before spinal anesthesia. The Group A or Group B drugs were premixed to

a total volume of 50 ml. with 0.9% NS and were administered intravenously as infusion over a 10 min period as a single-dose. Five minutes after the end of the infusion, the patients were placed in the left lateral position and lumbar puncture performed at the L3-L4 interspace using a standard midline approach with a 25-G Quincke spinal needle. Hyperbaric Bupivacaine 0.5% 3 ml (15 mg.) was injected intrathecally and the patients received oxygen 5 L/min throughout the procedure by Hudson facemask. Recordings were done by the same anesthesiologist from the beginning of the procedure till 24 hours after completing the surgery. Parameters observed will be:

Hemodynamic status

Heart Rate (HR), Mean Blood Pressure (MAP), Oxygen Saturation (SpO_2), and Respiratory Rate (RR) were recorded before premedication, 5 min after premedication, immediately before and after dural puncture, and every 5 min for first 60 min, every 10 min next 60 min and every 15 min for next 60 min after spinal anesthesia. Vasopressor and anticholinergic drug requirements were noted.

Hypotension (defined by a decrease in MAP below 20% of baseline or systolic pressure < 90 mm Hg) were treated with intravenous Ephedrine 6 mg and Ringer Lactate solution of 200 ml over a 5 minute period. Bradycardia of HR < 50 beats/min was treated with intravenous atropine 0.6 mg intravenously.

Sensory blockade

Onset of action of Sensory blockade after spinal anesthesia was assessed at every 2 min for the first 15 min or until two consecutive levels of sensory blockade were identical (i.e. fixation of the level) and thereafter every 10 min during surgery and postoperatively using pinprick sensation bilaterally in the mid-axillary line. Time for maximum sensory level was noted. Recovery time for sensory blockade defined as regression of anesthesia from the maximum level was recorded. Time for sensory regression of two dermatomes was noted. The time for the first request for analgesia and the number of patients who required supplemental analgesia was recorded.

Quality of sensory block

Postoperative pain was assessed by the patient using the Visual Analog Scale or VAS scale postoperatively. Patients with a VAS score of 3 or more received Inj. Diclofenac 1 mg/kg. intramuscularly. The time for first request for postoperative analgesia and number of patients who required supplemental analgesia were recorded.

Motor blockade

Onset of Motor blockade was assessed every 2 min for the first 15 min or till blockade of Modified Bromage Scale 3 is noted, whichever was earlier. Motor blockade duration is the time for return to Modified Bromage Scale 1.

Modified Bromage Scale

Bromage 0: Patients is able to move hip, knee & ankle;

Bromage 1: Patients is unable to move hip, but able to move knee & ankle;

Bromage 2: Patient is unable to move hip & knee but able to move ankle;

Bromage 3: Patient is unable to move hip, knee & ankle.

Ramsay Sedation Score

The scores were reevaluated every 10 min for up to 120 min. Excessive sedation recorded as a score greater than 4:

1. Patient is anxious and agitated or restless or both;
2. Patient is cooperative, oriented and tranquil;
3. Patient responds to commands only;
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus;
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus;
6. Patient exhibits no response.

The presence of any complication in the preoperative and postoperative periods was noted, particularly in relation to respiratory or cardiovascular problems, nausea or vomiting and headache.

Statistical analysis

The raw data was entered and mean and standard deviation values were analyzed using Microsoft Office Excel Worksheet (.xlsx) 2016 on Microsoft Windows 10 and p - value was analyzed using unpaired t - test in GraphPad InStat 3 (Trial). For statistical significance a p - value of 0.05 or lesser is taken as being statistically significant.

Results

All patients were comparable for age, weight and height and the difference was statistically not significant in both groups, shows in (Table 1).

Heart rate decreased in both the groups after spinal anesthesia, but the fall in heart rate in (Dexmedetomidine) Group A was statistically significant than with (Midazolam) Group B with the *p* - values as mentioned, shown in (Fig. 1).

Table 1: Demographic details in present study

Parameters	Group A	Group B	*p* - value	Statistical significance
No. of patients	50	50	–	–
Age (in years)	40.78 ± 6.27	38.44 ± 6.17	0.0629	Not significant
Weight (in kgs)	67.88 ± 7.95	69.66 ± 7.93	0.2532	Not significant
Height (in cms)	160.40 ± 5.31	159.96 ± 4.93	0.6686	Not significant

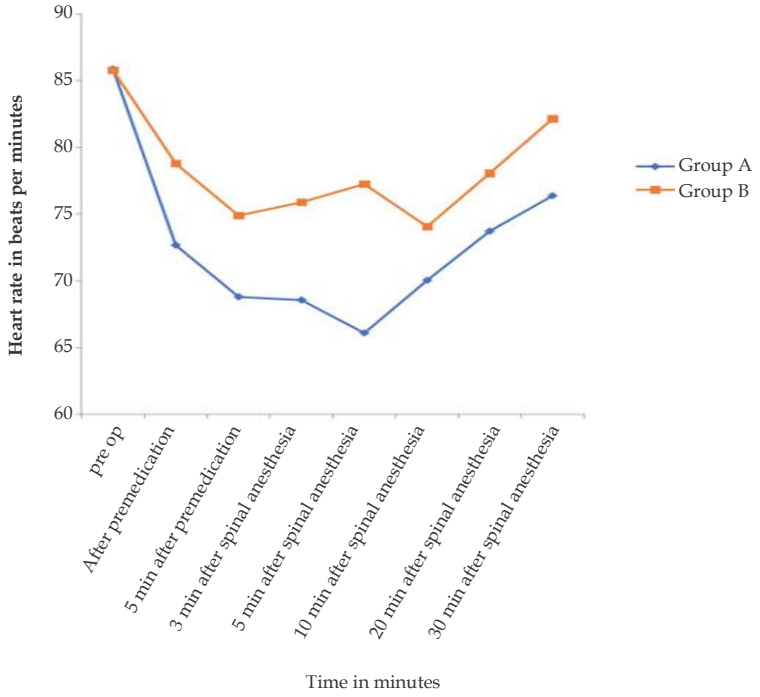

Fig. 1: Heart rate variation between two groups in present study

Mean arterial pressure decreased in both the groups after spinal anesthesia, but the fall in (Dexmedetomidine) Group A was statistically significant than with (Midazolam) Group B, shown in (Fig. 2 and Table 2).

Table 2: Time period during observation post operatively

Duration	Group A	Group B	*p* - value	Statistical significance
Time for onset of sensory blockade	228 ± 25.56	224 ± 35.31	0.517	Not significant
Two segment regression time (in min)	134.02 ± 25.26	110.72 ± 22.64	< 0.0001	significant
Motor blockade duration (in min)	175 ± 14.56	162 ± 15.48	< 0.0001	significant
First request of analgesia (in min)	230.52 ± 21.52	203.14 ± 24.99	< 0.0001	significant

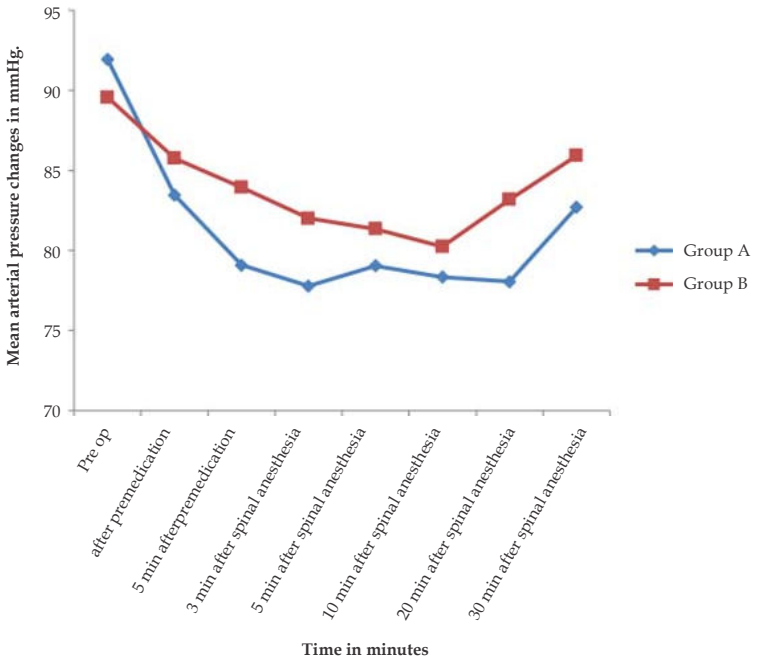

Fig. 2: Mean Arterial pressure variation between two groups in present study

Time for onset of sensory blockade is insignificant when compared in both groups.

On Comparision of side-effects in two groups it is observed insignificant, as shown in Table 3.

Table 3: Comparision of side-effects in two groups

Side-effects	Group A	Group B	Statistical significance
Bradycardia	8%	8%	Not significant
Hypotension	8%	8%	Not significant
Nausea/Vomiting	6%	6%	Not significant
Respiratory depression	0%	0%	Not significant

Discussion

Different drugs have been used as adjuvants with local anesthetic agents in order to prolong the duration of spinal anesthesia. Clonidine an α_2 agonist, has been widely used in the intrathecal, oral and intravenous routes to prolong the duration of spinal anesthesia. It is known to have prolonging effect on sensory and motor blockade when used as an oral premedication within 2 hours before bupivacaine spinal anesthesia. The intravenous administration of clonidine within 1 hr after the spinal blockade prolonged bupivacaine spinal analgesia for approximately 1 hour without adverse effect.[4]

Dexmedetomidine, also an α_2-agonist, 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. It has been used as adjuvant to local anesthesia in the intrathecal route and has significant effect on onset and duration of spinal anesthesia.

Dexmedetomidine has an onset of action of 30 min when the maintenance dose is used intravenously. Use of standard loading dose (1 μg/kg/hr infused over 10 minutes), decreases the time for onset of action. Side-effects of dexmedetomidine, such as hypotension and bradycardia, are dose dependent. Infusion of loading dose over 10 min and then infusing the maintenance dose decreases the incidence of those side-effects. Jorm CM, Stamford

JA found that dexmedetomidine has an inhibitory effect on the locus ceruleus (A6 group) located at the brain stem.[5] This supraspinal action could explain the prolongation of spinal anesthesia after intravenous administration of dexmedetomidine. The noradrenergic innervation of the spinal cord arises from the noradrenergic nuclei in the brain stem including the locus ceruleus, the A5 and the A7 noradrenergic nuclei. Neurons in the locus ceruleus are connected to the noradrenergic nuclei in the brain stem. Axon terminals of the noradrenergic nuclei reach lamina VII and VIII of the ventral horns of the spinal cord.

The activity of the noradrenergic neurons is decreased by agonists acting at α_2-adrenergic receptors on the locus ceruleus cell bodies. Therefore, inhibition of the locus ceruleus results in disinhibition of the noradrenergic nuclei and exerted descending inhibitory effect on nociception in the spinal cord.

The mechanism of motor blockade is unclear, the analgesic effects of α_2-adrenergic agonists could be mediated through supraspinal, spinal and peripheral actions.[6] Dexmedetomidine results in direct inhibition of impulse conduction in the large, myelinated Aα fibers and the 50% effective concentration (EC50%) measured approximately 4-folds of that in small, unmyelinated C fibers. This could explain the lesser duration of motor blockade compared with sensory blockade, as conduction of motor nerve fibers was less inhibited than sensory nerve fibers at the same concentration of dexmedetomidine. This would explain the prolongation of sensory blockade than motor blockade. Dexmedetomidine is known to have sedative effect providing better conditions for the surgeon and the patient. This study indicated that premedication with intravenous dexmedetomidine prolonged the duration of bupivacaine induced sensory blockade during spinal anesthesia. In addition, dexmedetomidine increased the time until first request of analgesic for postoperative pain relief. It also provided sedation comparable to midazolam premedication. It is recommended to administer dexmedetomidine over 10 min, as rapid administration might produce tachycardia or bradycardia, hypotension.[7]

Furthermore, previous studies describe an evaluation of the analgesic effect of different doses of intravenous dexmedetomidine (0.25, 0.5 and 1 mcg/kg.) on ischemic pain in healthy volunteers demonstrated moderate analgesia with a ceiling effect at 0.5 mcg/kg. With this in mind, dexmedetomidine, 0.5 mcg/kg was given intravenously over 10 min in this study. Administration of midazolam 0.05 mg/kg. was reported to give enough sedation and amnesia without any adverse effects on hemodynamics and respiration in patients aged 30–70 yrs, under spinal anesthesia.[8] Therefore, midazolam 0.05 mg/kg was given intravenously over 10 min in this study.

Midazolam has been reported to have an antinociceptive effect through the neuroaxial pathway. However, the effects of midazolam on nociception may depend on the route of administration, with analgesia observed after spinal or epidural application, but not after systemic administration of this agent.[9] In this study also, intravenous administration of midazolam did not enhance the analgesic effect of intrathecal injection. Finally, the use of dexmedetomidine premedication before spinal anesthesia seems to offer clinical advantages compared with midazolam premedication, since dexmedetomidine provides additional analgesia. During lumbar puncture, it is preferable that patients be able to alert the anesthesiologist of any paresthesia and pain on injection, both of which have been associated with postoperative neurologic deficit.

Midazolam may cause restlessness and disinhibition instead of sedation in some patients and this is referred to as a paradoxical reaction.[10] Thus, surgery will then become extremely difficult. In this study, no patients experienced a paradoxical reaction with midazolam. The sedation produced by dexmedetomidine differs from other sedatives, as patients may be easily aroused and remain cooperative.[11] Midazolam has a potent anterograde amnesic effect, and dexmedetomidine infusion also may result in impairment of memory and psychomotor performance. However, the amnesic effect of midazolam rapidly diminished with time.

Rapid or bolus intravenous administration of dexmedetomidine produces sudden hypotension and bradycardia until the central sympatholytic effect dominates, resulting in moderate decreases in both MAP and HR from baseline. This study observed no significant cardiovascular variability in this study consisting mainly of healthy patients. This might be attributed to sympathetic blockade associated with spinal anesthesia, slow administration of a low-dose and sufficient preoperative hydration. However, further studies are needed to investigate the efficacy of dexmedetomidine in geriatric patients or medically compromized patient populations. In previous studies, it has been shown that dexmedetomidine

caused no or minimal respiratory depression. However, midazolam is known to cause apnea and arterial desaturation in sedative doses. In this study, there was no respiratory depression in any patients and respiratory parameters remained within normal limits throughout the procedure.

Nevertheless, it was concluded within the constraints of the present design that the addition of intravenous dexmedetomidine before spinal blockade provided similar pain relief with delayed-onset of postoperative pain and significantly less analgesic requirements.

In this study, we have shown that a single-dose of intravenous dexmedetomidine given as premedication prolonged the duration of sensory blockade of bupivacaine induced spinal anesthesia. It also provided sedation and additional analgesia The heart rate decreased significantly after the start of intravenous infusion loading dose and extended in the PACU. This decrease in the heart rate was clearer and more significant in Group A in comparison with Group B. The lower heart rate observed in Group A could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by dexmedetomidine.[12] Other studies support the finding that the bradycardia effect of dexmedetomidine is long lasting when used as a premedication drug. In conclusion, supplementation of spinal anesthesia with intravenous dexmedetomidine produces significantly longer sensory and motor blockade than intrathecal bupivacaine along with intravenous midazolam. Adverse side-effects were avoided by the slow infusion of loading dose of dexmedetomidine. All patients reached good sedation levels that enabled their cooperation and better operating conditions for the surgeon without significant respiratory depression.

Conclusion

Intravenous dexmedetomidine premedication prolongs the duration of sensory and motor blockade during the spinal anesthesia with Bupivacaine with good sedation and postoperative analgesia than with intravenous midazolam premedication in patients undergoing gynecological surgeries under spinal anesthesia.

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