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ORIGINAL ARTICLE

A STUDY TO EVALUATE THE EFFICACY OF DIFFERENT DOSES OF INTRATHECAL DEXMEDETOMIDINE WHEN USED AS AN ADJUVANT TO BUPIVACAINE IN PATIENTS UNDERGOING HYSTERECTOMY

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ABSTRACT: BACKGROUND: Intrathecal adjuvants have gained popularity with the aim of prolonging the duration of block and quality of analgesia. Dexmedetomidine is relatively selective alpha2-agonist with sympatholytic, sedative, amnestic and analgesic properties. The study is designed to evaluate the efficacy of intrathecal administration of different doses of dexmedetomidine on duration of subarachnoid block and postoperative analgesia. **METHODS**: 60 female patients scheduled for hysterectomy, randomized in 3 groups of 20 each. Each patient was given 2.5ml of 0.5% bupivacaine with 5µg of dexmedetomidine in Group-A, 7.5µg in Group-B and 12µg in Group-C. Onset and regression time of sensory and motor block, hemodynamic change, sedation score, requirement of rescue analgesics and incidence of adverse effects were assessed perioperatively upto 24hours. **RESULTS:** Demographic data was statistically comparable. Sensory block onset was statistically highly significant between Group-A & C and Group-B & C ($p>0.05$). The time for 2 segment sensory regression and bromage scale 0 was increased by adding dexmedetomidine in a dose dependent manner ($p<0.001$).Postoperative VAS and analgesic requirement was significantly lower in Group-C ($p<0.001$). Sedation scores were significantly higher in Group-C ($p<0.05$). A significant decrease in heart rate and blood pressure was observed by increasing dose of dexmedetomidine with respect to base line in all the three groups. However, the results were comparable on intergroup analysis. **CONCLUSION:** Dexmedetomidine when used as an adjuvant to intrathecal bupivacaine hastens the onset of sensory block prolongs the duration of sensory and motor block in a dose dependent manner without any significant increase in side effects.

KEYWORDS: Dexmedetomidine, Bupivacaine, Intrathecal, adjuvant.

INTRODUCTION: Surgery is physical and psychological stress and many patients experience significant amounts of pain and discomfort in the postoperative period. Abdominal hysterectomy is referred among the most frequent procedures associated to pain in the gynecologic population.[1]

Visceral afferent fibers from the uterine corpus transmit pain signals to the brain by entering the spinal cord at the T11-T12 levels, whereas spinal cord levels S2-S4 receive signals from the cervix, vagina, and perineum.[2]

Various intrathecal adjuvants to local anesthetics have been found to improve the quality as well as prolongation of duration of spinal anesthesia. Alpha-2 agonists are known to reduce anesthetic requirements, and because of their sympatholytic properties, provide hemodynamic stability during the perioperative period. Dexmedetomidine is a highly selective alpha-2 adrenergic agonist; its IV use has shown to be effective for providing sedation, anxiolysis and analgesia in a dose dependent manner.[3]

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The intrathecal or epidural use has been studied in animal models without any neurological complications.[4, 5]

Even after extensive study of the drug, the optimal intrathecal dose of dexmedetomidine remains unknown. This study was planned to evaluate the optimal dose of dexmedetomidine that would be effective for its intrathecal use.

MATERIALS AND METHODS: This randomized, prospective, double-blind study approved by the local Ethics committee was conducted on 60 patients in age group of 25-60 years belonging to ASA I and II undergoing elective hysterectomy under spinal anesthesia. Exclusion criteria included the patients on alpha adrenergic receptor blockers, local sepsis at the site of proposed puncture, patient with known hypersensitivity to study drug, patients being treated with anticoagulants, CNS active drugs, patients suffering from bleeding diathesis or coagulation disorders, spinal deformity or tuberculosis spine, increased intracranial pressure, patients with some psychiatric history, patients with neurological disease with motor and sensory deficit. Patients were randomly allocated into three groups of 20 patients each; Group A: 5μg of dexmedetomidine, Group B: 7.5μg of dexmedetomidine and Group C: 12μg of dexmedetomidine with 2.5ml of 0.5% hyperbaric bupivacaine.

Patients were premedicated preoperatively with tab. alprazolam 0.25mg and tab. ranitidine150mg on night prior and on the day of surgery. Patients were kept fasting as per the standard guidelines. In the operation theatre, baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR), oxygen saturation (SpO2) and electrocardiography (ECG) were recorded. Patients were preloaded with Ringer's Lactate solution @10ml/kg. Subarachnoid block was performed in sitting or left lateral position, at L2-L3/L3-L4 intervertebral space. The onset and duration of sensory blockade was assessed by using pinprick test. Motor blockade was assessed using modified bromage scale. The time to reach T10 dermatome sensory block, peak sensory level, and achieving Bromage scale of 3 were recorded.

The regression time for sensory and motor block were recorded in a post anesthesia care unit (PACU). Pulse rate (PR), systolic (SBP) and diastolic blood pressure (DBP) and oxygen saturation (SpO2) were recorded every 2min for first 10 min, every 5 min for next 20 min and every 15 min intraoperatively and till the discharge from PACU. A decrease of 30% in blood pressure from baseline was defined as hypotension and treated with ephedrine 6mg boluses. Bradycardia was defined as decrease in heart rate of more than 20% from baseline and treated with boluses of 0.3 mg atropine. Postoperatively patients were observed for 24 hours and time of first analgesic administration on demand recorded and adverse effects such as nausea, vomiting, hypotension, bradycardia and sedation were recorded. The level of sedation was evaluated perioperatively using Ramsay sedation scale.

Statistical Analysis: Data was analyzed using computer statistical software system SPSS® version 16 (Statistical Packages for the Social Sciences, Chicago, IL). Results are expressed as mean and standard deviation (SD), median and range or numbers. The power of 0.95 and α error of 0.05 with primary analysis of power being done with regression time of sensory and motor blockade, duration of analgesia, VAS and dosage of rescue analgesia. Statistical analysis was done with chi square test nonparametric data and student's t test for parametric data. Intergroup analysis was done using

student t-test and intragroup analysis was done using paired t test. Values of $p<0.05$ considered as statistically significant, and values of $p<0.001$ were taken as highly significant.

RESULTS: 60 patients were enrolled in the study. The groups were statistically comparable with respect to age, weight, height, ASA physical status and duration of surgery (Table 1).

The time of sensory onset was statistically highly significant between group A & C and group B & C ($p<0.001$) but comparable between group A & B ($p>0.05$). The mean time to achieve modified bromage scale 3 was found to be statistically insignificant among all the three groups ($p>0.05$). The time to two segment regression, motor block regression to modified bromage scale 0 were highly significantly prolonged in group C as compared to group A and group B ($p<0.001$) (Table 2). The duration of analgesia was significantly prolonged in group C (412 mins) & B (310 mins) than in group A (200 mins) ($p<0.001$) (Table 2). So group C & B had significantly longer time to first analgesic requirement on demand (Table 2).

During perioperative period haemodynamic variables were measured and a significant reduction in pulse rate and blood pressure was seen when compared to baseline. Significant decrease in heart rate was observed starting at 15 min until 150 mins in group A and at 10 min until 195 min group B and at 10 min until 210 min in group C ($p<0.05$) (Fig1). Systolic blood pressure showed a significant decrease starting at 15 min until 60 min in group A, starting at 10 min until 90 min in group B and at 10 min until 105 min in group C ($p<0.05$) (Fig 2). However, on intergroup analysis haemodynamic parameters were found to be statistically comparable among all the three groups ($p>0.05$).

The mean VAS score among all the three groups was statistically insignificant till 90 min postoperatively ($p>0.05$). An increase in VAS was seen after 105 minutes in group A, 240 minutes in group B and 480 minutes in group C (Fig 4). The time of the first rescue analgesic requirement was significantly prolonged in group C as compared to group B and A ($p<0.05$) (Table 2, Fig 5). The mean total consumption of rescue analgesia in first 24 hours was significantly decreased in Group C (502±7.6 mg) as compared to group B (630±8.4 mg) and group A (900±4.5 mg) ($p<0.001$) (Table 3, Fig 5). The mean sedation score among the groups remained statistically comparable until 15 min ($p>0.05$), after which it became significantly more in group C as compared to group A & B ($p<0.05$). (Fig. 6)

Four patients in group A, 5 in group B and 7 in group C experienced hypotension. One patient in group A and 3 each in group B & C received ephedrine but total IV ephedrine used was not statistically significant among all the three groups ($p>0.05$). Bradycardia was observed in 1 each patient in group A & B and 2 patients in group C and was treated with IV atropine. Total dose of atropine was statistically insignificant among all the three groups ($p>0.05$). Other side effects such as nausea, vomiting, dry mouth, pruritus, respiratory depression and urinary retention was found to be statistically insignificant ($p>0.05$).

DISCUSSION: The postoperative period is to provide subjective comfort in addition to inhibiting trauma-induced nociceptive impulses in order to blunt autonomic and somatic reflex responses to pain.[6] The use of adjuvant drugs for regional anesthesia had been intended to prolong the duration of local anesthetic agents. A large number of adjuvants to local anaesthetics for spinal anaesthesia such as epinephrine, phenylephrine, adenosine, magnesium sulphate, benzodiazepines, ketamine,

neostigmine and opioids have been used.[7] The last two decades have witnessed a dramatic increase in the use of alpha-2 agonists.

Their use in the perioperative period have been associated with reduced anaesthetic requirement and attenuated heart rate (HR) and blood pressure (BP) response to stressful events[8]. Dexmedetomidine, a highly selective α2-adrenoceptor agonist with a relatively high ratio of α2/ α 1-activity, possesses all these properties but lacks respiratory depression,[9] making it a useful and safe adjunct in diverse clinical applications. As a neuraxial adjuvant, α2-adrenoceptor agonists can stimulate a number of antinociceptive mechanisms depending on the dose and the route of administration; however, the main site for their antinociceptive effect in physiological pain conditions seems to be the spinal dorsal horn.[9]

Intraoperatively it decreased the onset of sensory and motor block and prolongs the duration of block significantly when used with bupivacaine in a dose dependent manner. However hemodynamically, there was a fall in blood pressure and heart rate in all the three groups with respect to baseline. This can be explained on the basis of biphasic blood pressure response i.e. a short hypertensive phase and subsequent hypotension. The two phases are considered to be mediated by two different alpha2-adrenergic receptor subtype; the alpha 2B receptor is responsible for initial hypertensive phase whereas hypotension is mediated by alpha 2A receptor.[10] This was further substantiated by comparable intergroup comparison.

Postoperative pain assessment was done by VAS which was significantly reduced at different time intervals in a dose dependent manner. Requirement for first rescue analgesia was delayed with higher dose of dexmedetomidine. This could be due to the complementary or synergistic action of dexmedetomidine as an additive to local anesthetics. Local anesthetics act by blocking sodium channels, α2 adrenoreceptors agonist act by binding to the presynaptic C-fibres and post synaptic dorsal horn neurons. They produce analgesia by depressing release of C-fiber transmitters and hyperpolarization of post synaptic dorsal horn neurons.[11-13]

In our study we observed some adverse effects such as hypotension, bradycardia, nausea and vomiting with dexmedetomidine but the results were statistically comparable.[14, 15] The observed heart rate response seems to be a combination of a baroreflex mediated reduction in heart rate, centrally mediated reduced sympathetic tone and increased vagal tone. Nausea and vomiting might be associated with the hypotensive episodes or increased increased vagal tone after sympathetic blockade.[16] Sedation scores also increased with escalating the dose. However, no incidence of respiratory depression was seen in any of the groups.

Limitations of our Study were:

- Small sample size,
- Several randomized control trials are available on intrathecal use of dexmdetomidine in the literature; though its intrathecal use is not approved.

Thus we concluded that addition of dexmedetomidine improves the quality and duration of postoperative analgesia and also provide the analgesic sparing effect when used with hyperbaric bupivacaine intrathecally in a dose dependent manner. A significant fall in hemodynamics with respect to baseline was observed in all the three groups and for a longer duration in patients who had received higher dose of dexmedetomidine. Thus, we suggest an intrathecal dose of 7.5μg as an

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optimal dose for providing prolonged postoperative analgesia with lesser hemodynamic variations and without increasing incidence of significant adverse effect.

Variables	Group A n=20	Group B n=20	Group C n=20	Significance
Age (years)	46.35±9.103	46.05±8.249	45.50±8.971	NS
Weight (kg)	68.70±7.491	69.60±8.444	68.95±6.219	NS
Height (cm)	157.50±2.819	158.55±3.379	157.35±4.017	NS
Duration of surgery(min)	79.25±15.600	82.75±10.062	81.00±15.694	NS

Table 1: Demographic data

Data: mean±SD. NS- Non significant (p>0.05).

Characteristics of block	Group A N=20	Group B N=20	Group C N=20	Statistical significance
Sensory block to reach T10 (min)	2.15±0.745	2.20±0.410	1.55±0.510	A to C-HS A to B-NS B to C-HS
Motor block to reach bromage 3 (min)	3.10±0.852	3.30±1.031	2.75±1.020	NS
2 seg. Sensory regression (min)	104.7±25.5	145.10±24.5	220.65±25.8	HS
Motor Regression to bromage 0 (min)	243.8±22.0	305.4±35.8	387.0±39.4	HS
Duration of analgesia (min)	200.0±26.8	310.0±65.8	412.7±68.4	A to B-S A to C-HS B to C-S

Table 2: Block onset time, time to reach motor bromage scale 0, sensory and motor regression time in minutes

Data: mean±SD. NS- Non significant (p>0.05), HS-Highly Significant (p<0.001), S-Significant (p<0.05)

	Group A	Group B	Group C
Total dosage (mg)	900±4.5	630±8.4	502±7.6

Table 3: Total dosage of rescue analgesic in first 24 hour

Data: mean±SD.

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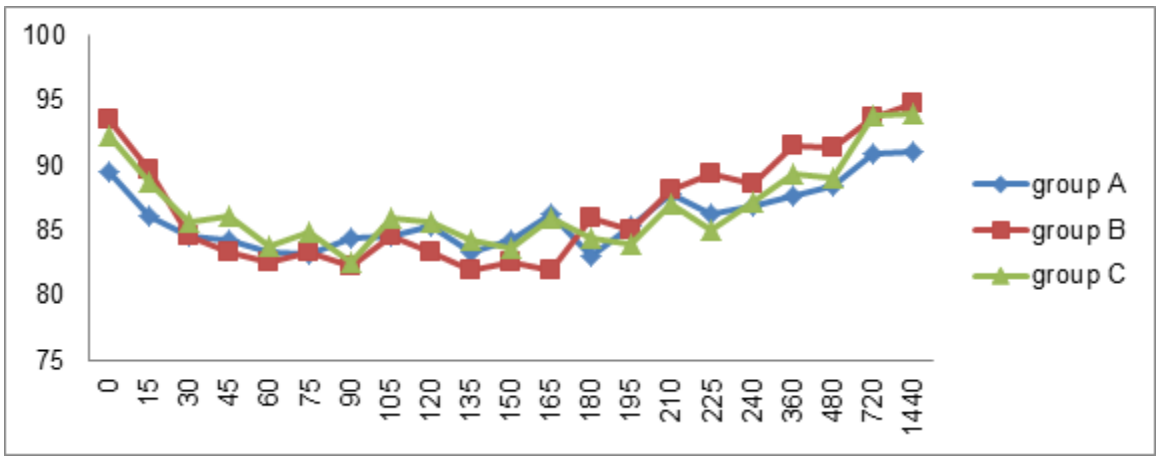

Fig. 1: Perioperative pulse rate at various time intervals

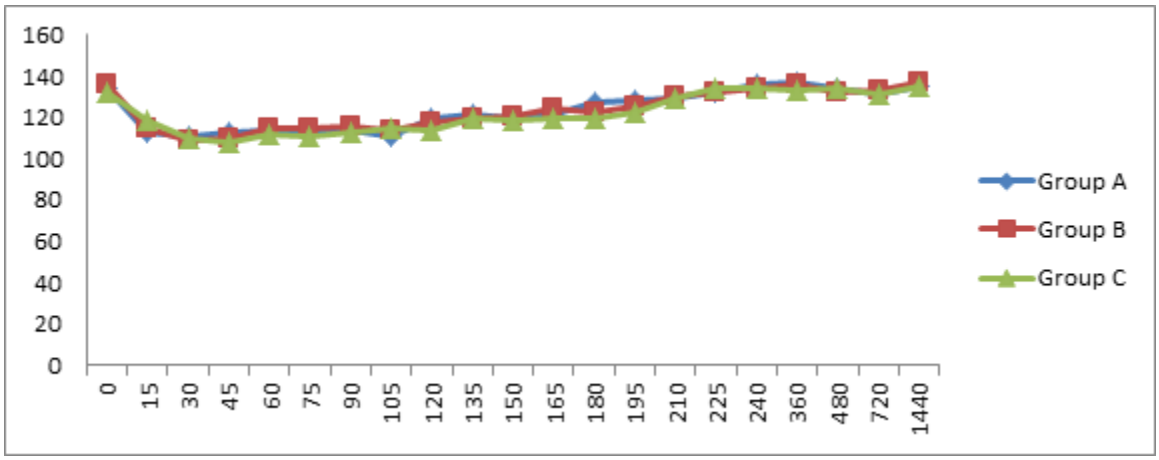

Fig. 2: Perioperative systolic blood pressure at various time intervals

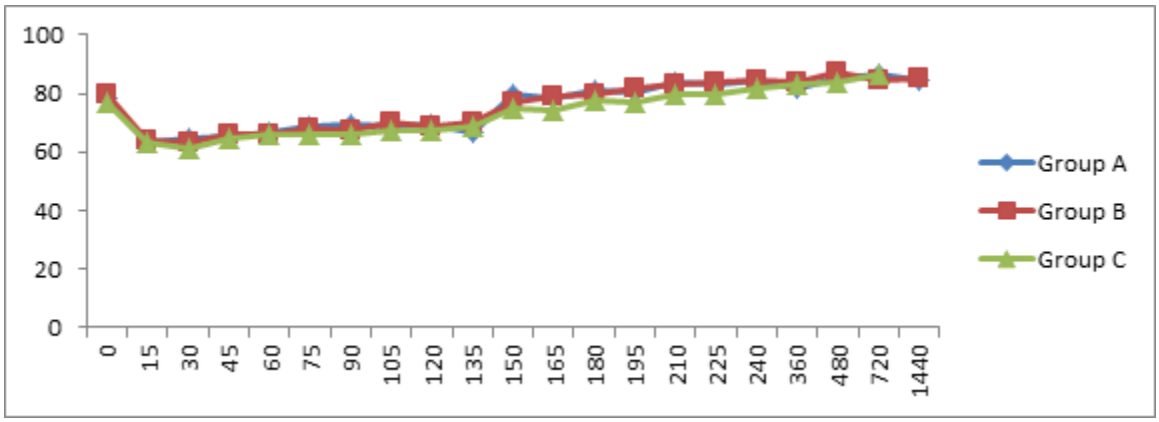

Fig. 3: Perioperative diastolic blood pressures at various time intervals

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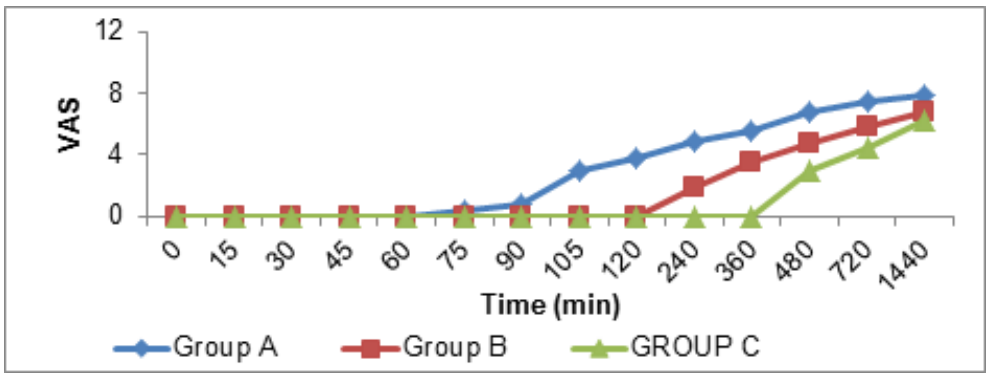

Fig. 4: Visual Analogue Scale at various time intervals postoperatively

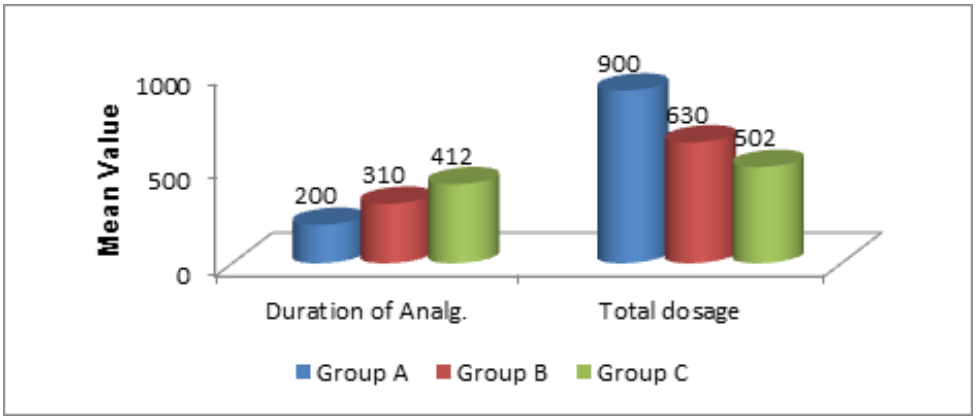

Fig. 5: Duration of analgesia and Total dosage of rescue analgesia

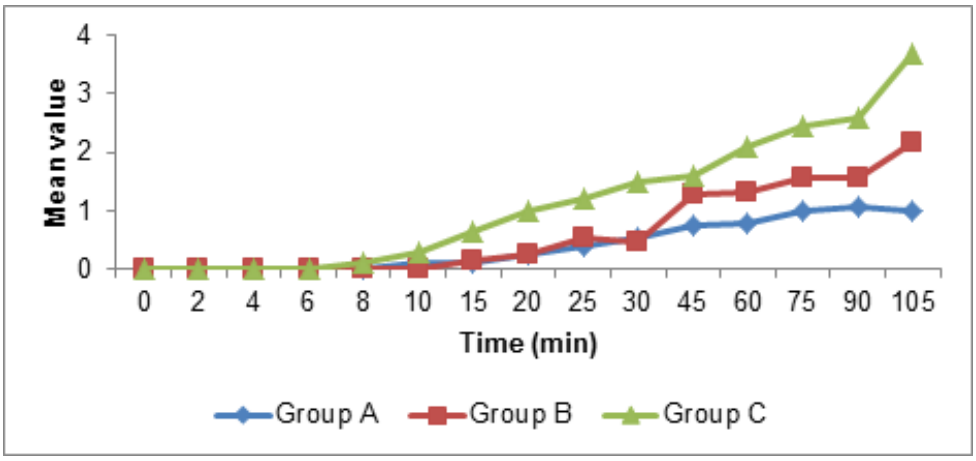

Fig. 6: Sedation scores in the groups intraoperatively

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