

## **A comparison of intrathecal dexmedetomidine and clonidine as adjuvants to hyperbaric bupivacaine for gynecological surgery**

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### **ABSTRACT**

**Background:** Various adjuvants are being used with local anesthetics for prolongation of intraoperative and post-operative analgesia. Dexmedetomidine, a highly selective alpha<sub>2</sub> adrenergic agonist, is a new neuraxial adjuvant gaining popularity. The purpose of this study was to compare the onset, duration of sensory and motor block, hemodynamic effects, post-operative analgesia, and adverse effects of dexmedetomidine and clonidine with hyperbaric 0.5% bupivacaine for spinal anesthesia.

**Methods:** 60 patients belonging to ASA Grade 1 and 2 undergoing elective gynecological surgery under spinal anesthesia were studied in this prospective. The patients were allocated in two groups (30 patients each). Group bupivacaine + clonidine (BC) received 17.5 mg of bupivacaine supplemented 45 mcg clonidine and Group bupivacaine + dexmedetomidine (BD) received 17.5 mg bupivacaine supplemented 5 mcg dexmedetomidine. The onset time of sensory and motor level, time to reach peak sensory and motor level, the regression time of sensory and motor level, hemodynamic changes, and side effects were recorded.

**Results:** Patients in Group BD had significantly longer sensory and motor block time than patients in Group BC. The onset time to reach dermatome T<sub>4</sub> and modified Bromage<sub>3</sub> motor block were not significantly different between two groups. Dexmedetomidine group showed significantly less and delayed requirement of rescue analgesic.

**Conclusion:** Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability and reduced demand of rescue analgesic in 24 hrs as compared to clonidine.

**Keywords:** Alpha<sub>2</sub> adrenergic receptor agonist, Bupivacaine, Clonidine, Dexmedetomidine, Spinal anesthesia, Group BC=bupivacaine + clonidine, Group BD=bupivacaine + dexmedetomidine

### **INTRODUCTION**

The anesthesia of choice most commonly used for gynecological surgery is regional anesthetic technique. Various adjuvants are being used with local anesthetics for prolongation of intraoperative and post-operative analgesia.

Most of the clinical studies about the intrathecal alpha<sub>2</sub> adrenergic agonist are related to clonidine.<sup>1</sup> Dexmedetomidine, the highly selective alpha<sub>2</sub> adrenergic agonist, is used for various procedures in the perioperative period.<sup>2</sup> Based on earlier human studies, intrathecal 5 mcg dexmedetomidine would produce longer duration of analgesic effect in spinal anesthesia with minimal side

effects.<sup>4-7</sup> Where gradually evolving studies can build the evidence for its safe use in central neuraxial blocks.<sup>3</sup>

We explore its usefulness and also compare this new alpha<sub>2</sub> adrenergic agonist with the previously established and widely used adjuncts.

### **METHODS**

We select 60 adult females belonging to ASA Grades 1 and 2 scheduled for gynecological surgery under subarachnoid block, were enrolled in this prospective and randomized study. Patients with contraindication to regional anesthesia, history of significant co-existing diseases, such as ischemic

heart disease, hypertension, impaired renal function, severe liver disease, neurological problems, and mental retarded women, were excluded from the study.

All patients were examined and investigated a day prior to surgery. We teach them visual analog scale (VAS)<sup>8</sup> and it was used for measuring the post-operative pain.

**Intraoperative**

In the operation theater intravenous line (IV) was secured and all patients were pre-loaded with ringer lactate 10 ml/kg. Electrocardiogram, pulse oxymeter, and non-invasive blood pressure (BP) were attached, and baseline parameters were recorded.

The study solutions were prepared in 5 ml syringe. The subarachnoid block was administered in L<sub>2-3</sub> or L<sub>3-4</sub> intervertebral space using a 23G spinal needle with patients in left lateral position under all aseptic precautions. Patients were made supine following the block.

The onset and duration of sensory block and motor block, time to complete motor block recovery, and duration of spinal anesthesia were recorded. The onset of sensory block was defined as the time between injection of intrathecal anesthetic and the absence of pain at the T4 dermatome assessed by pinprick every 2 mins until T4 dermatome was achieved (Table 1).

The duration of sensory block was at the time of regression of two segments in the maximum block height, evaluated by pinprick. The motor level was assessed according to modified Bromage score.<sup>9</sup>

**Bromage score**

Score:

- 0: the patient is able to move the hip, knee, and ankle
- 1: the patient is unable to move the hip but is able to move the knee and ankle
- 2: the patient is unable to move hip and knee but is able to move the ankle
- 3: the patient is unable to move hip, knee, and ankle.

Time for motor block onset was defined as modified Bromage score of 3. Complete motor block recovery was assumed when modified Bromage score was 0.

The duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the post-operative period.

Surgery was allowed to commence on achieving adequate sensory block (T4). All vitals were recorded before intrathecal injection; 5, 10, 15, and 20 mins after intrathecal injection and subsequently every 15 mins until the end of

**Table 1: Grouping for the study.**

Group BC	Intrathecal bupivacaine 17.5 mg (3.5 ml)+ Clonidine 45 mcg (0.3 ml)+preservative free normal saline (0.2 ml)
Group BD	Intrathecal bupivacaine 17.5 mg (3.5 ml)+ dexmedetomidine 5 mcg (0.05 ml)+ preservative free normal saline (0.45 ml)

BC: Bupivacaine clonidine, BD: Bupivacaine dexmedetomidine

surgery. Pain score (VAS) was recorded after surgery in post-operative period. IV fluids were given to maintain the BP.

Hypotension was defined as a decrease in systolic BP by 30% from baseline and was treated with IV cristalloid fluids or 6 mg of bolus mephentermine.

Heart rate (HR) <50 beats/mine was corrected using IV glycopyrrolate (0.2 mg). The incidence of nausea, vomiting, and sedation were recorded. De Kock sedation scale<sup>10</sup> was used: 1=patient somnolent but responding to verbal commands; 2=patient somnolent, not responding to verbal commands but responding to manual stimulation; and 3=patient somnolent, not responding to verbal commands or manual stimulation.

**Post-operative**

Motor block recovery (modified bromage score of zero) and sensory block regression were assessed every 15 mins after completion of surgery until the time of regression of two segments in maximum block in the post-operative room along with the vital signs and VAS scores. Any patient showing VAS more than or equal to 3 was administered the supplemental dose of IM diclofenac (75 mg). The amount required by the patients in the next 24 hrs was recorded in both the groups.

**Statistical analysis**

Data obtained were tabulated and analyzed using Microsoft Office spreadsheet program, Excel. Data were expressed as means, standard deviations, ranges, numbers, and percentages. For categorical covariates (sex, ASA class, hypotension, bradycardia, etc.), the Z test was used as appropriate with p values reported at 95% confidence interval.

The p value was considered as significant if it was <0.05.

**RESULTS**

The number of patients under each type of gynecological surgery performed was similar among the groups, thereby keeping the comparison unbiased.

There was no statistical difference in patient’s demographics or duration of surgery as shown in Table 2. Table 3 shows

the number of patients in each group undergoing different types of gynecological surgeries.

When compared the time of onset of both sensory and motor block, was statistically insignificant in two groups ( $p > 0.05$ ) (Table 4). Patients in Groups bupivacaine + dexmedetomidine (BD) and bupivacaine + clonidine (BC) had time of onset of sensory block was  $3.11 \pm 0.06$ ,  $2.88 \pm 0.78$  mins after the injection, respectively. T4 was the highest level of sensory block attained at  $7.8 \pm 1.54$ ,  $8.1 \pm 1.36$  mins after injection in group BD and BC, respectively.

Duration of sensory and motor block was significantly prolonged in BD as compared to group BC ( $p < 0.001$ ) ( $p < 0.038$ ). The duration of spinal anesthesia was shorter in group BC as compared to group BD ( $p < 0.00001$ ) (Table 4).

**Table 2: Patient's demographics.**

Variable	Group BC	Group BD	p value
Age (years)	45.2±9.4	42.4±5.4	>0.05
ASA (1:2)	26:4	28:2	>0.05
Height (cm)	170.6±5.61	69.6±5.5	>0.05
Weight (kg)	69.3±10.7	66.6±7.9	>0.05
Duration of surgery (min)	120±33.7	115.5±34.5	>0.05

ASA: American society of anesthesiology, values are mean±SD, all patients (n=60) completed the study, SD: Standard deviation, BC: Bupivacaine clonidine, BD: Bupivacaine dexmedetomidine

**Table 3: Type of gynecological surgeries.**

Type of gynecological Surgery performed	Group BC (n=30)	Group BD (n=30)
Abdominal hysterectomy	12	15
Vaginal hysterectomy	10	8
Tubal recanalization	5	5
Laparotomy for ovarian mass	3	2

BC: Bupivacaine clonidine, BD: Bupivacaine dexmedetomidine

**Table 4: Characteristics of spinal anesthesia.**

Variable (min)	Group BC	Group BD	p value
Time of onset of sensory block	2.88±0.78	3.11±0.06	>0.05
Time of onset of motor block	4.44±0.52	4.22±1.20	>0.05
Time to reach max. sensory level	8.11±1.36	7.88±1.53	>0.05
Duration of sensory block	258.66±35.93	348.66±74.3	0.001
Duration of motor block	305.33±36.91	387.11±105.14	0.038
Duration of spinal anesthesia	360±30	524.66±49.75	0.00001

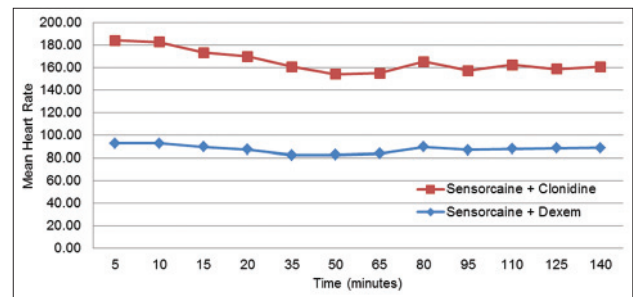
The mean values of mean arterial pressure and HR were comparable between the two groups throughout the intra-operative and post-operative period (Figures 1 and 2). None of the patients experienced respiratory distress at any point of time. SpO<sub>2</sub> of all the patients were greater than 96% at all the times and did not require additional oxygen in post-anesthesia room.

Three patients in Group BD and six patients in Group BC had bradycardia and required treatment with glycopyrrolate 0.2 mg IV. Four patients in Group BD and six patients in Group BC had significant hypotension which was treated with mephentermine 6 mg IV. There was no incidence of respiratory depression, nausea, and vomiting in both groups.

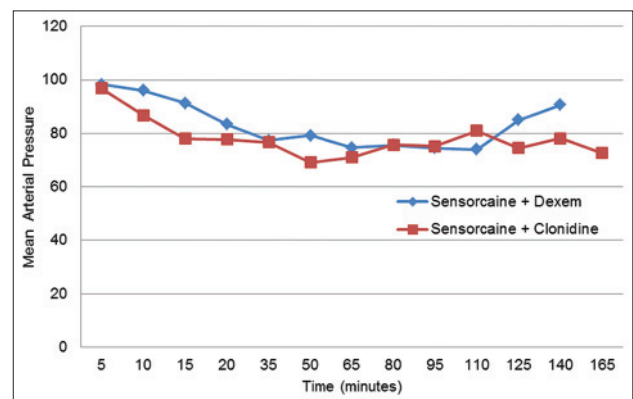
Lower VAS values (<3) were observed in both the groups during the whole duration of surgery. None of the patients required additional analgesics intraoperatively. Post-operative VAS scores and total analgesic requirement in 24 hrs were minimal in Group BD ( $p < 0.05$ ).

**DISCUSSION**

In our study, we compared dexmedetomidine and clonidine for gynecological surgery. We evaluated the analgesic efficacy of intrathecal dexmedetomidine. The results of our study show that supplementation of spinal bupivacaine with 5 mcg dexmedetomidine significantly prolonged both sensory and motor block compared with 45 mcg clonidine. The quality of analgesia significantly improved with the use of dexmedetomidine as an adjuvant compared to clonidine.



**Figure 1: Heart rate values versus time.**



**Figure 2: Mean arterial pressure versus time.**

The mechanism by which intrathecal alpha2 adrenoreceptor agonists prolong the motor and sensory block of local anesthetics is at the best, speculative. It may be an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetics and intrathecal alpha2 adrenoreceptor agonists. Local anesthetics act by blocking sodium channels. Alpha2 adrenoreceptor agonists act by binding to the presynaptic C-fibers and post-synaptic dorsal horn neurons. They produce analgesia by the depressing release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons.<sup>4,5,11</sup> The complementary action of local anesthetics and alpha2 adrenoreceptor agonist accounts for their profound analgesic properties. The prolongation of motor block of spinal anesthetics may be the result of binding of alpha2 adrenoreceptor agonists to the motor neurons in the dorsal horn.<sup>4,5</sup> Dexmedetomidine is eight times more specific and highly selective alpha2 adrenoreceptor agonist compared to clonidine, thereby making it a useful and safe adjunct in the diverse clinical application.<sup>12,13</sup> It is observed in various studies that dexmedetomidine as an epidural adjuncts prolong the motor/sensory block duration time and post-operative analgesia without any additional morbidity.<sup>14,15</sup> Clinical studies exhibit potentiation of neuraxial local anaesthetics, decrease in intraoperative anaesthetic requirement with prevention of intraoperative awareness, improved intra-operative oxygenation, and postoperative analgesia when epidural or caudal dexmedetomidine was used in conjunction with general anaesthesia.<sup>16-18</sup>

Most of the clinical experience gained in the use of intrathecal alpha2 adrenoreceptor agonists has been described with clonidine.<sup>19-22</sup>

In our study, the intrathecal dose of dexmedetomidine selected was based on previous human studies wherein no neurotoxic effects have been observed.<sup>4,6</sup> Kanazi et al.,<sup>4</sup> found that 3 mcg dexmedetomidine or 30 mcg clonidine added to 13 mg spinal bupivacaine produced the same duration of sensory and motor block with minimal side effects in urological surgical patients. On the basis of this, we assumed that 3-5 mcg of dexmedetomidine is potent to 30-45 mcg clonidine when used for supplementation of spinal bupivacaine.

Time of onset of sensory blocks was comparably similar in both groups. These findings were in concordance with the results of Al-Ghanem et al., who observed no difference in the onset time in patients receiving dexmedetomidine (7.5±7.4 mins) and fentanyl (7.4±3.3 mins) as adjuvant to isobaric bupivacaine (p=0.95). The onset times observed in a study conducted by Al-Ghanem et al., were relatively longer than that observed by us.

The intrathecal 5 mcg dexmedetomidine used in our study had shown comparable onset of motor block with significantly prolonged duration of motor block (305.33±36.91) (which is in consonance with the results

observed by investigators in comparison to various adjuvants used in their studies).<sup>4-7,23</sup> when compared to the duration of motor block of 250±76 mins in Kanazi et al.'s, study (p<0.001) and 240±64 mins in Al-Ghanem et al.'s, study (p<0.001). Hala EA Eid et al.,<sup>24</sup> observed dose dependent prolongation of motor and sensory blockade with reduced analgesic requirement with increasing dosage of intrathecal dexmedetomidine.

The most significant side effects reported about the use of intrathecal alpha2 adrenoreceptor agonists are bradycardia and hypotension. In the present study, these side effects were not significant probably because we used a small dose of intrathecal dexmedetomidine and clonidine with local anesthetics.<sup>25</sup> These doses of adjuvants used in our study did not affect the near maximal sympatholysis caused by local anesthetics. Small dosages of adjuvants may also be responsible for minimal or no sedation observed in any of the group in the study.

Intrathecal alpha2 adrenoreceptor agonists have been found to have an antinociceptive action for both somatic and visceral pain. Both dexmedetomidine and clonidine provide good quality of intra-operative analgesia and hemodynamic stability. Visceral pain usually occurs during abdominal surgery under spinal anesthesia. Intrathecal dexmedetomidine and clonidine added to local anesthetic reduce both visceral and somatic pain in our study as no patient's perceived visceral pain in both BD and BC groups.

Fukasima et al., administered 2 mcg/kg epidural dexmedetomidine for post-operative analgesia in humans but did not report neurological deficits. Our study has shown that addition of 5 mcg dexmedetomidine with hyperbaric bupivacaine significantly prolongs both sensory and motor block. The analgesia was significantly better in Group BD as compared to Group BC and it was statistically significant. A small dose of intrathecal dexmedetomidine (5 mcg) used in combination with bupivacaine in humans has been shown to shorten the onset of motor block and prolong the duration of motor and sensory block with hemodynamic stability and lack of sedation (7) Al-Ghanem et al. Mahendru et al., study shows that the use of intrathecal dexmedetomidine as an adjuvant to bupivacaine seems it to be an attractive alternative to fentanyl and clonidine for long duration surgical procedures.<sup>26</sup>

In our study, hypotension was more in the clonidine group than in the dexmedetomidine group, but it was not statistically significant. A 4 weeks follow-up showed that intrathecal dexmedetomidine at a dose of 5 mcg was not associated with any new onset of back, hip or leg pain, weakness, or neurological deficit.

## CONCLUSION

Our study report shows that the use of intrathecal dexmedetomidine as an adjuvant to bupivacaine seems it

to be an attractive alternative to clonidine for long duration surgical procedures due to its profound intrathecal anesthetic and analgesic properties combined with minimal side effects. In the dexmedetomidine group, we found the longer duration of motor and sensory block, stable hemodynamic condition, and good patient satisfaction.

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