Original Article

Dexmedetomidine versus midazolam as adjuvants to intrathecal bupivacaine: A clinical comparison

Usha Shukla[1], Tallamraju Prabhakar[2], Kiran Malhotra[3], Dheeraj Srivastava[4]

Departments of [1,3]Anaesthesiology and Critical Care and [4]Community Medicine, U. P. Rural Institute of Medical Sciences and Research, Saifai, Etawah, [2]Department of Anaesthesiology and Critical Care, Era Medical College, Lucknow, Uttar Pradesh, India

Abstract

Background and Aims: Trials are being carried out to identify an adjuvant to intrathecal bupivacaine that preferably potentiates postoperative analgesia .This prospective, randomized, double-blind study was aimed to compare the onset and duration of sensory and motor block, postoperative analgesia and adverse effects of dexmedetomidine or midazolam given with 0.5% hyperbaric bupivacaine for spinal anesthesia.

Material and Methods: A total of 80 patients, scheduled for vaginal hysterectomies, were randomly allocated to Group D ($n = 40$) to receive intrathecally 3.0 mL 0.5% hyperbaric bupivacaine +5 ug dexmedetomidine in 0.5 mL of normal saline; and Group M ($n = 40$) to receive 3 mL of 0.5% hyperbaric bupivacaine +2 mg midazolam in 0.4 mL (5 mg/mL) +0.1 mL normal saline. The onset, duration of sensory and motor block, time to first postoperative analgesia and side effects were noted. Power and Sample size (PS) version 3.0.0.34 was used for power and sample size calculation. Statistical analysis was performed using Microsoft (MS) Office Excel software with the Student's *t*-test and Chi-square test (level of significance $P = 0.05$).

Results: Duration of sensory, motor blockade and time to the first requirement of analgesia were significantly higher in Group D. Postoperative visual analog scale was significantly less in Group D than Group M. Both groups were similar with respect to sedation, hemodynamic variables and side-effects.

Conclusion: Intrathecal dexmedetomidine was better adjuvant than midazolam as it produces significantly longer duration of sensory block, reduced doses of postoperative analgesic agents with comparable side-effects.

Key words: Dexmedetomidine, intrathecal injections, midazolam

Introduction

Regional anesthesia (spinal or epidural anesthesia) is a preferred technique for vaginal hysterectomies and perineal surgeries.[1] However, local anesthetic agents if used alone have relatively shorter duration of action and early analgesic intervention is required in the postoperative period. To prolong the postoperative analgesia, many adjuvants have been tested and tried,[2] but the adverse effects produced by them, limit their use as adjuvant. Trials are still underway to compare the benefits and disadvantages of one adjuvant over the other.

Midazolam is well-known to potentiate the analgesic effects of local anesthetic agents and has antinociceptive properties without producing significant side-effects.[3,4]

Dexmedetomidine, an α-2 adenoreceptor agonist is relatively a new intrathecal adjuvant to local anesthetic agents. It provides good intra-operative analgesia and prolongs postoperative

Address for correspondence: Dr. Usha Shukla,
Type - V, 201, New Campus, U. P. Rural Institute of Medical Sciences and Research, Saifai, Etawah, Uttar Pradesh, India.
E-mail: ushashukla1970@gmail.com

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analgesia with stable hemodynamic conditions and is associated with minimal side-effects.[5-7]

The aim of this study was to compare and evaluate the onset and duration of sensory and motor block, postoperative analgesia and side-effects if any, when either dexmedetomidine 5 μg or midazolam 2 mg is added to hyperbaric bupivacaine 0.5% given intrathecally in patients undergoing elective vaginal hysterectomies.

Material and Methods

After getting approval by our Institutional Medical Ethics Committee for the study protocol and obtaining written informed consent from each patient, we conducted this prospective, randomized, double blind study. Eighty patients of American Society of Anesthesiologists (ASA) physical Status I and II, in the age group of 35-60 years, scheduled to undergo elective vaginal hysterectomies under subarachnoid block (SAB) were included. Patients having body weight >110 kg, height <140 cm, on calcium channel blockers, adrenergic receptor blockers, arrhythmias, having heart block, and contraindications to spinal anesthesia (e.g., coagulation defects, infection at the puncture site, preexisting neurological deficits in the lower limbs) were excluded from the study. Patients with known allergy to study drugs and local anesthetics and patients with respiratory, neurological, psychological, hepatic or renal diseases were also excluded from the study.

No premedication was given to patients. On the arrival of the patients in the operating room, all patients were monitored for heart rate (HR), noninvasive blood pressure, respiratory rate (RR), pulse-oximetery (oxygen saturation [SpO_2]), electrocardiography and baseline values were recorded. An intravenous (i/v) line was secured with 18G cannula and all patients were preloaded with 10 mL/kg of Ringer Lactate solution. Following preloading, under all aseptic precautions, lumber puncture was performed with 25G Quincke's spinal needle in L3-L4 interspace or L4-L5 interspace (if lumber puncture was found to be difficult at L3-L4 interspace) through a midline approach in a sitting position. The observers as well as the patients were blinded to the drug solution and patients' group. The study solution was prepared by anesthesiology staff, who was not involved in administration of study drugs as well as recording the parameters. By sealed envelope technique, patients were randomly allocated to two groups. Patients allocated to Group D (n = 40) received 3 mL 0.5% hyperbaric bupivacaine +5 μg dexmedetomidine in 0.5 mL of normal saline intrathecally (dexmedetomidine 100 μg/mL was diluted in preservative free normal saline) and Group M (n = 40) received 3 mL 0.5% hyperbaric bupivacaine +2 mg preservative free midazolam in 0.4 mL (5 mg/mL) +0.1 mL of normal saline intrathecally.

The study solution was administered over 10-15 s through spinal needle with no barbotage. After SAB, patients were placed in lithotomy position and oxygen 2 L/min was given through the face mask.

The level of sensory and motor block was assessed every 2 min for first 15 min, at 20 min, 30 min after completion of intrathecal injection of the drug and then every 15 min during surgery and in the postoperative period in post anesthesia care unit (PACU). The level of sensory block was assessed by pin prick method using 26G hypodermic needle along mid axillary line. Sensory block at level of T8 dermatome was considered as adequate for surgery.

The onset of sensory block (defined as the time interval from completion of subarachnoid drug injection to onset of complete loss of needle prick sensation at T8 level), time to achieve peak sensory block level, level of the sensory block (highest dermatomal level of sensory blockade by needle prick method), and duration of sensory block (defined as time interval from completion of subarachnoid drug injection to two segment regression of sensory block by needle prick method) and regression of sensory block to S1 level was also recorded.

Motor block was assessed using modified Bromage scale.[8] Score 0: Patient able to move the hip, knee and ankle. Score 1: Patient unable to move the hip but able to move the knee and ankle. Score 2: Patient unable to move the hip and knee but able to move the ankle. Score 3: Patient unable to move the hip, knee and ankle.

Onset of motor blockade (time interval from completion of subarachnoid drug injection to Bromage score 3) and duration of motor blockade (time interval from Bromage score 3 to Bromge score 0) were also noted.

All calculations of durations were done considering the time of subarachnoid injection as time "zero." All patients were shifted from PACU only when regression of sensory block occurred to S1 level and Bromage score of 0 was achieved.

The level of sedation[7] assessed before giving SAB and then assessment was repeated every 15 min intra-operatively and postoperatively using following score. Score 0: Alert. Score 0: Occasionally drowsy, easy to arouse. Score 0: Frequently drowsy, easy to arouse. Score 0: Somnolent, difficult to arouse.

Heart rate, mean arterial pressure (MAP), SpO_2, were recorded every 5 min for 1 h and then every 15 min till 2

segment regression of sensory block. Hypotension was defined as decrease in MAP >20% from baseline or fall of systolic blood pressure below 90 mm of Hg and was treated with ephedrine 6 mg in incremental doses followed by i/v fluids as required. Bradycardia was defined as decrease in HR >20% from baseline values or <50 beats/min (bpm) and was treated with boluses of atropine 0.3-0.6 mg i/v.

Intra-operatively, all patients were assessed for nausea, vomiting, sedation, rescue analgesia. Intra-operative rescue analgesia was planned to be given with injection fentanyl 1 μg/kg i/v, if required. If pain still not subsided, general anesthesia was given and the patient was excluded from the study. Duration of surgery (min), infused volume of i/v fluids (mL), doses of ephedrine (mg) and atropine (mg) were also recorded.

Postoperatively, pain was assessed using visual analogue scale (VAS; 0- no pain; 10- worst pain) at 1, 2, 3, 4, 8, 12, 24 h. Patients who had VAS score of 3 or more were given injection diclofenac 75 mg intramuscularly. The time to first request of analgesia and total number of diclofenac injections required in 24 h was also recorded.

In postoperative period, all patients were closely observed for 24 h for any side effects, e.g., behavioral changes, confusion, dizziness, nystagmus, dry mouth, nausea, vomiting or any neurological complication such as numbness or pain in leg, back and buttocks, incontinence or retention of urine.

A sample size of 40 patients per group (Group D, Group M) was calculated using power and sample size calculation (PS version 3.0.0.34 Power and sample size calculator. PS version 3.0.34 available at http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize assessed on 20.10.2013.). For this, an error of 0.05 and power of 80% was defined to calculate the above sample size.

Statistical analysis was performed using MS Office Excel software Microsoft. Microsoft Excel. Redmond, Washington: Microsoft, 2003. Computer Software. Results were expressed as mean ± standard deviation, median, range or numbers and percentage (%). Normally distributed parameter data was assessed using unpaired student *t*-test. The comparison was carried out using Chi-square test (χ^2) with a "*P* value" reported at 95% confidence interval. The level of significance used was $P = 0.05$.

Results

The study groups (Group D and M) were found to be comparable with respect to patient's characteristics such as age, weight, height, ASA physical status, duration of surgery and i/v fluid administered. [Table 1]. Spinal anesthesia was successful in all the patients in both groups and no patient in either group required rescue analgesia (fentanyl) or general anesthesia.

Characteristics of sensory and motor block are summarized in Table 2. Median peak sensory block level achieved in both the study groups was $T_{6,}$ with the range of T_3-T_9 in Group D and T_4-T_9 in Group M. No statistically significant difference was found in Group D and M with respect to time to reach peak sensory block level (*P* 0.990). The onset of sensory and complete motor block was found to be comparable between both the study groups (*P* 0.095; *P* 0.281 respectively). The regression of sensory and motor blockade in dexmedetomidine group (Group D) was significantly longer when compared with midazolam group (Group M) as shown by 2 segment regression time, (*P* 0.0013) regression time to S1 level, (*P* 0.000) duration of motor block from Bromage score 3 to Bromage score 0 (*P* 0.000) [Table 2].

Time to first postoperative analgesia was significantly longer in Group D when compared to Group M (*P* 0.000). On statistical analysis, maximum pain score on VAS and number of diclofenac injections required in first 24 h were significantly less in Group D as compared to Group M (*P* 0.000; *P* 0.000 respectively) [Table 2]. The mean HR [Figure 1] and MAP [Figure 2] was found to be comparable in both the study groups.

Table 1: Patient's demographic and intra-operative data

Variables	Group D (*n* = 40) Mean ± SD	Group M (*n* = 40) Mean ± SD	*P* value
Age (years)	49.0±10.3	48.8±9.8	*T*=0.09, df=78, *P*=0.092
Weight (kg)	58±9.2	57.8±8.0	*T*=0.10, df=78, *P*=0.917
Height (cm)	151±7.2	152±8.0	*T*=0.59, df=78, *P*=0.558
ASA I/II#	26/14	23/17	—
Duration of surgery (min)	62±26.8	65.0±24.2	*T*=5.3, df=78, *P*=0.6000
I/V fluid	890±210	896±216	*T*=0.13, df=78, *P*=0.090
Dose of epedrine required (mg)	10.0±1.65	8.9±4.0	*T*=1.60, df=78, *P*=0.943

Values are expressed as mean ± SD. #Values are expressed as numbers. SD = Standard deviation, ASA = American Society of Anesthesiologists, i/v = Intravenous

Table 2: Study parameters — characteristics of sensory and motor blockade and data recording postoperative analgesia

Variables	Group D (n = 40)	Group M (n = 40)	P value
	Mean ± SD	Mean ± SD	
Peak sensory block level*	T6 (T3-T9)	T6 (T4-T9)	—
Time to reach peak sensory level (min)	11.9±1.6	10.9±2.1	T=2.39, df=42, P=0.990
Time to reach sensory block level to T8 (min)	7.2±1.2	6.80±0.9	T=1.69, df=78, P=0.095
Time to reach complete motor block level (Bromage score 3) (min)	7.0±1.0	6.80±0.6	T=1.08, df=78, P=0.281
2 segment regression time (min)	126.4±14.2	116.2±7.2	T=4.06, df=78, P=0.0013
Regression time to S1 level (min)	320.8±50.2	220.4±70.4	T=7.25, df=78, P=0.0000
Duration of motor blockade (Bromage score 0) (min)	246.0±68.0	152.2±2.9	T=8.72, df=78, P=0.0000
Time to first postoperative analgesia (min)	380.0±18.0	220.1±14.8	T=43.4, df=78, P=0.0000
Pain score on VAS (0-10)	4.2±1.1	6.4±2.0	T=6.10, df=78, P=0.0000
Number of diclofenac injection required in first 24 h	0.90±0.16 (0-1)	2.60±0.39 (1-3)	T=14.97, df=78, P=0.000

*Values are expressed as mean ± SD. *Peak sensory block levels are shown as median (range). VAS = Visual analogue scale, SD = Standard deviation*

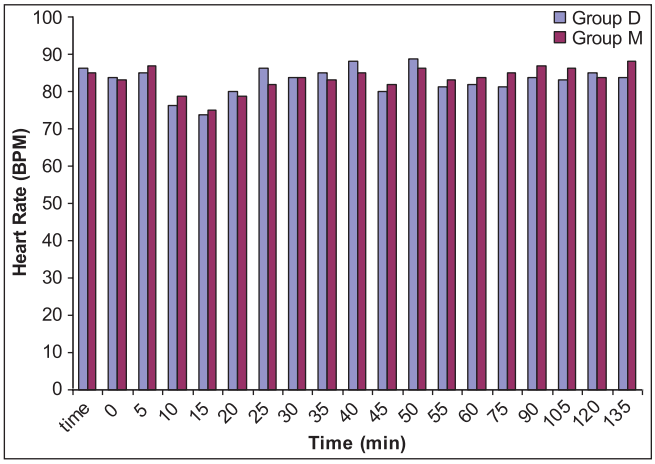

Figure 1: Heart rate (bpm) values are the mean ± standard deviation

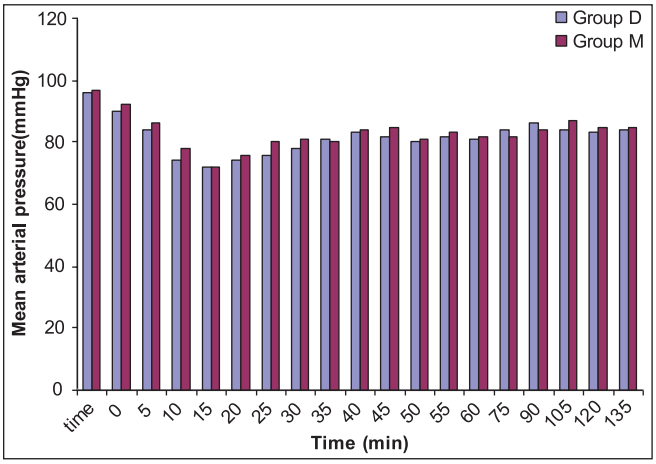

Figure 2: Mean arterial pressure (mmHg) values are the mean ± standard deviation

Respiratory parameters (SpO_2 and RR) were found to be within normal limits in intra and postoperative period. The sedation score was between 0 and 1 in both the study groups during intra and postoperative period.

The overall incidence of adverse/side effects was found to be similar among study groups (P 0.595) [Table 3]. Hypotension and bradycardia was mild to moderate in both the study groups except in Group D, in which only 1 patient had blood pressure of <80 mm of Hg, and required 12 mg ephedrine to maintain her blood pressure.

All patients in both study groups had complete recovery of sensory and motor functions. No patient in either group had any neurological impairment like pain or numbness in leg, back or buttock, incontinence or retention of urine, headache in postoperative period or thereafter.

Discussion

Clonidine is most widely researched intrathecal α-2 adrenergic agonist and its synergistic use with local anesthetic agents is well-known.[9]

Dexmedetomidine, an imidazoline compound, is a D- isomer of medetomidine, which is pharmacologically active and exhibits selective α-2 adenoceptor agonistic activity.[10,11] From earlier studies,[5-7] we assumed that 5 μg dexmedetomidine would produce prolonged sensory blockade with bupivacaine 0.5% in spinal anesthesia with less side effects. Dexmedetomidine binds to presynaptic C-fibers and postsynaptic dorsal horn neurons. Intrathecal dexmedetomidine produces analgesia by suppressing the release of C-fibers pro nociceptive neurotransmitters, substance P and glutamate from primary afferent terminals and by hyper polarization of postsynaptic dorsal horn neurons through G- protein mediated activation of potassium channels.[12] An α-2 agonist, administered intrathecally or epidurally, provides prolonged analgesic effect in postoperative period without severe sedation.[13,14] The absence of severe sedation is due to sparing of supraspinal sites from excessive drug exposure resulting in intense analgesia without heavy sedation.[15]

Many studies[3-4,16,17] done in the past, revealed that Midazolam is safe and efficacious as an adjuvant to bupivacaine hence we

Table 3: Adverse/side effect

Variables	Group D (n = 40)	Group M (n = 40)	P value
	Mean ± SD (%)	Mean ± SD (%)	
Hypotension	8 (20)	5 (12.5)	χ^2=2.32, df=3, P=0.5095
Bradycardia	8 (20)	4 (10)	
Nausea	2 (5)	1 (2.5)	
Dizziness	1 (2.5)	3 (7.5)	

Values are expressed as numbers (%). SD = Standard deviation

used midazolam 2 mg as an adjuvant to bupivacaine 0.5% in SAB. Goodchild *et al.*[18] have found that intrathecal midazolam is involved in the release of endogenous opioids acting on spinal delta receptors so antinociceptive effects of morphine like substances is potentiated when intrathecal midazolam is added.

This study indicates intrathecal administration of 5 μg dexmedetomidine as an adjuvant to hyperbaric bupivacaine 0.5% significantly prolongs the duration of both sensory and motor blockade without producing significant side effects compared with intrathecal midazolam 2 mg in patients undergoing vaginal hysterectomies under SAB. Kanazi *et al.*[7] studied 60 patients, undergoing transurethral resection of the prostate or bladder tumor under SAB with bupivacaine and found that 3 μg dexmedetomidine produced shorter onset of motor blockade with prolonged duration of sensory and motor block with minimal side-effects. Al-Ghanem *et al.*[5] also found that 5 μg dexmedetomidine used intrathecally produces significantly prolonged sensory and motor blockade when compared to intrathecal fentanyl 25 μg. In present study also, we found similarly prolonged duration of sensory and motor block.

Kim and Lee[16] and Prakash *et al.*[19] observed analgesic effects of intrathecal midazolam 1 mg or 2 mg along with bupivacaine and concluded that duration of postoperative analgesia was significantly prolonged with the addition of intrathecal midazolam in a dose dependent manner. Our study also reports prolonged duration of sensory and motor blockade in midazolam group (Group M).

Visceral and somatic pain, nausea and vomiting are very commonly encountered intra-operative problems in female genital tract surgeries under spinal anesthesia with local anesthetic agents.[20] Al-Ghanem *et al.*[5] and Kalso *et al.*[21] have reported that an α-2 receptor agonists, when added to spinal anesthetic agents, significantly reduce visceral and somatic pain. Kim and Lee[16] and Bharti *et al.*[22] found out that intrathecal midazolam also reduces visceral and somatic pain during intra-operative period. In our study also, both dexmedetomidine and midazolam improved the intra-operative analgesia, as no patient in either of the study group suffered from visceral or somatic pain intra-operatively and also no patient in both the study groups required additional analgesia or general anesthesia.

The most significant side effects associated with the use of intrathecal α-2 receptor agonists are hypotension and bradycardia. In this study, 8 patients (20%) had hypotension and 8 patients (20%) had bradycardia in Group D, while in Group M, 5 patients (12.5%) had hypotension and 4 patients (10.0%) had bradycardia, but overall analysis showed that this difference was not significant statistically (P 0.0595). Hypotension and bradycardia, both could be managed with Ephedrine and Atropine, respectively. This can be explained by the fact that we used smaller doses of dexmedetomidine. Previous studies[5,6] have also revealed the prolongation of spinal block by intrathecal 5 μg and 10 μg dexmedetomidine without significant effect on blood pressure and HR.

Intrathecal α-2 receptor agonists and midazolam, both have intra-operative sedative effects, but similar to Tamsen and Gordh[15] and Bharti *et al.*[22] no patients in either group were heavily sedated as is evident by overall sedation level between 0 and 1.

Dexmedetomidine given intrathecally as an adjuvant to bupivacaine leads to increase in the duration of motor blockade, limiting its use in short term surgical procedures or ambulatory surgeries.

Although no major side-effects were reported in this study, larger studies are required to rule out any short term or long term adverse effects. The study population included was otherwise healthy and young patients and the effect in old patients with cardio vascular co-morbidities or other medically compromised population are yet to be investigated.

Conclusion

In vaginal hysterectomies, intrathecal use of dexmedetomidine was found to be better alternative to intrathecal midazolam, since it produces significantly longer duration of sensory block as is evident by significantly prolonged postoperative analgesia, reduced pain scores on VAS and reduced number of doses of postoperative analgesics without being associated with significant hemodynamic instability, sedation and other side effects.

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Conflicts of interest

There are no conflicts of interest.

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