Effect of Adding Dexmedetomidine versus Fentanyl to Intrathecal Bupivacaine on Spinal Block Characteristics in Gynecological Procedures: A Double Blind Controlled Study

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Abstract: Problem statement: The purpose of this study was to evaluate the onset and duration of sensory and motor block as well as operative analgesia and adverse effects of Dex Metedo Midine (DXM) or fentanyl given intrathecally with plain 0.5% bupivacaine for spinal anesthesia. **Approach:** seventy six patients classified as American Society of Anesthesiologists (ASA) status I, II and III scheduled for vaginal hysterectomy, vaginal wall repair and tension free vaginal tape were prospectively studied. Patients were randomly allocated to receive intrathecally either 10 mg isobaric bupivacaine plus 5 µg dexmetedomidine (group D n = 38) or 10 mg isobaric bupivacaine plus 25 mg fentanyl (group F n = 38), the onset time to reach peak sensory and motor level, the regression time for sensory and motor block, hemodynamic changes, and side effects were recorded. **Results:** Patients in group D had significant longer sensory and motor block times than patients in group F. the mean time of sensory regression to S1 was 274±73 min in group D and 179±47 min in group F (P < 0.001). The regression time of motor block to reach modified Bromage 0 was 240±60 min in group D and 155±46 min in group F (P< 0.001). The onset times to reach T10 dermatome and to reach peak sensory level as well as onset time to reach modified Bromage 3 motor block were not significantly different between the two groups. **Conclusion:** In women undergoing vaginal reconstructive surgery under spinal analgesia, 10 mg plain bupivacaine supplemented with 5 µg dexmetedomidine produces prolonged motor and sensory block compared with 25 µg fentanyl.

Keywords: Dexmetedomidine, fentanyl, bupivacaine, spinal anesthesia

INTRODUCTION

Vaginal surgery including vaginal hysterectomy, tension free vaginal tape and vaginal repair are often done under regional anesthesia. Surgery on the uterus and other genital organs performed under epidural or spinal block is often accompanied by visceral pain, nausea and vomiting[1,2]. Fentanyl in various doses (10, 20, 30, 40 µg) when added to spinal bupivacaine increase the duration of analgesia and reduce intraoperative nausea and vomiting[3]. DXM is an α2-adrenoreceptor agonist that is approved as an intravenous sedative and coanalgesic drug. Its use is often associated a decrease in heart rate and blood pressure[4]. Intrathecal and epidural characteristics of DXM were studied in animals[5,6]. Most of the clinical studies about intrathecal α2 adrenoreceptor agonist are related to clonidine. There is little in the literature about the use of intrathecal DXM with local anesthesia in humans. Kanazi *et al.*[7] found that 3 µg DXM and 30 µg clonidine are equipotent intrathecally when added to bupivacaine in patients undergoing urology procedures. The same author found that DXM and clonidine produced significant short onset of sensory and motor block as well as significantly longer duration of sensory and motor block than bupivacaine alone without serious side effects. The aim of this study was to compare the effect of DXM 5µg versus fentanyl 25 µg on intraoperative analgesia and the duration of sensory motor block when added to 10 mg intrathecal plain bupvacaine.

MATERIALS AND METHODS

The protocol of the study was approved by the scientific search committee of the medical college and written consent was obtained preoperatively. Seventy eight patients (ASA I-III) scheduled for tension-free

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vaginal tape, vaginal wall repair, and vaginal hysterectomy under spinal anesthesia were included in this prospective randomized, double blinded study. Patients with uncontrolled, labile hypertension or patients with allergy to the study drugs were excluded from the study. Patients received no premedication, and upon arrival of patients into the operating room, ECG, pulse oximetry, and non invasive blood pressure were monitored. Following infusion of 500 mL Lactated Ringers solution and while the patient in the sitting position lumber puncture was performed at L3-L4 level through a midline approach using a 25-gauge Quincke spinal needle (B Braun medical, Germany). Using a computer generated random numbers, patients were allocated into 2 groups and group D received isobaric bupivacaine 10 mg and 5 µg DXM in 2.5 mLs. Group F received 10 mg isobaric bupivacaine and 25 µg fenatnyl into 2.5 mL. DXM (precedex 100µg mL^{-1} Abbott laboratory) were diluted in preservative free normal saline. After intrathecal injection, patients were positioned in lithotomy position and oxygen 2 Lmin^{-1} was given through a face mask. The doctor anesthetist performing the block was blinded to the study drug and recorded the intraoperative data. Vital signs were recorded at 5 min interval intraoperatively until the end of surgery. In the Post Anesthesia Care Unit (PACU), vital signs were recorded every 15 min. The sensory block level was assessed by cold alcohol swap along the midclavicular line bilaterally. The motor block was assessed according to the modified Bromage scale[8]: Bromage 0, the patient is able to move the hip, knee and ankle; Bromage 1, the patient is unable to move the hip but is able to move the knee and ankle; Bromage 2, the patient is unable to move the hip and knee but able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle. The times to reach T10 dermatome sensory block, peak sensory level and Bromage 3 motor block were recorded before surgery. The regression time for sensory and motor block were recorded in PACU. All durations were calculated considering the time of spinal injection as time zero. Patients were discharged from the PACU after sensory regression to S1 dermatome and Bromage 0. Assessment of pain intraoperatively and in PACU was done using visual analogue pain scale between 0-10 (0 = no pain, 10 = the most severe pain). Intraoperative nausea, vomiting, pruritus, additive analgesia and sedation were recorded. The following sedation scale was used: 0 = no sedation, 1 = mild sedation, 2 = moderate sedation, 3 = severe sedation. Hypotension was defined as a decrease in systolic blood pressure > 30% of the baseline value or systolic blood pressure < 100 mm Hg, hypotension was treated with intravenous

blouses of 6 mg ephedrine and crystalloid fluids. Bradycardia was defined as a pulse rate of < 50 beat/ min and was treated with boluses of 0.3- 0.5 mg atropine.

Statistical methods: Statistical analysis was done using statgraphics centurion XV (Statpoint, Herdon, Virginia-USA). Data was expressed as either mean and standard deviation or numbers and percentages. The demographic data of patients were studied for each of the three groups. Continues covariates (Age, BMI, gage and duration of surgery were compared using analysis of variance ANOVA. For categorical covariates (sex, ASA class, nausea/ vomiting, hypotension, bradycardia, use of ephedrine, use of additive analgesia, the use of atropine and type of surgery). The comparison was studied using chi-squared test or the Fisher's exact test as appropriate, with the p value reported at the 95% confidence interval. The level of significance used was p = 0.05.

To calculate the sample size, a power analysis of (α = 0.05 and β = 0.90) showed that 30 patients per study group were needed to detect an increase of 30 min difference between the median duration of spinal sensory block between the groups.

RESULTS

All patients (n = 76) completed the study; there was no statistical difference in patients' demographics or the duration and type of surgery as shown in Table 1. The onset time of sensory block to reach T10 dermatome was 7.5±7.4 min. for Group D and 7.4±3.3 min. for Group F (p = 0.95). The time to reach the maximal sensory block was 19.34+2.87 min. for group D and 18.39+2.46 min. for Group F (p = 0.126) The onset time of modified Bromage 3 motor block was also not different between group D and F; 14.4+6.7 and 14.3+5.7 min. respectively (P = 0.93). The regression time to reach modified Bromage 0 in Group D (240+64 min.) was significantly longer than that for group F (155+46 min.), p<0.001. The time reach S1 segment was significantly longer in group D (274.8+73.4 min.) than in group F (179.5+47.4 min.) (P < 0.001) Table 2. The peak sensory level was T6 (T4-T9) in group D and T6 (T3-T8) in group F, without significant difference between the group (p = 0.88).

The mean values of mean arterial blood pressure and heart rate were comparable among the 2 groups (figures 1and 2). The sedation score was between 0 and 1 in both groups. Side effects of spinal block are shown in Table 3. The overall side effects were significantly more in group F than in group D (P < 0.002).

Table 1: Patients demographics. Values are mean ± SD. BMI = body mass index. TVT= tension free vaginal tape

Variable	Group D (n = 38)	Group F (n = 38)
Age (yr)	49.0 ± 10.9	49.6 ± 11.6
BMI	29.1 ± 6.1	31.3 ± 6.2
ASA I, II, III	22,16,0	16,17,5
TVT, vaginal repair, vaginal hysterectomy	18,19,4	22,18,5
Duration of surgery (min)	51.6 ± 26.8	59.0 ± 25.7
Need for ephedrine	4	8
Dose of ephedrine (mg)	10.5 ± 1.73	12.37 ± 10.07
Need for atropine	1	2

Table 2: Characteristics of spinal block, data are shown as mean ± SD. The maximal sensory block level is given as median (range)

Variable	Group D (n= 38)	Group F (n= 38)	P value
Peak sensory block level	T6 (T4-T9)	T6 (T3-T8)	0.88
Time to reach T10 sensory block level (min)	7.5 ± 7.4	7.4 ± 3.3	0.95
Time to reach peak sensory)	19.34±2.87	18.39±2.46	0.126
Time to reach Bromage 3 motor block (min)	14.4 ± 6.7	14.3 ± 5.7	0.932
Regression time to S1 dermatome level (min)	274.8 ± 73.4	179.5 ± 47.4	< 0.001
Regression time to Bromage 0 (min)	240 ± 64	155 ± 46	< 0.001

Table 3: Adverse effects of spinal block. Values are numbers (%)

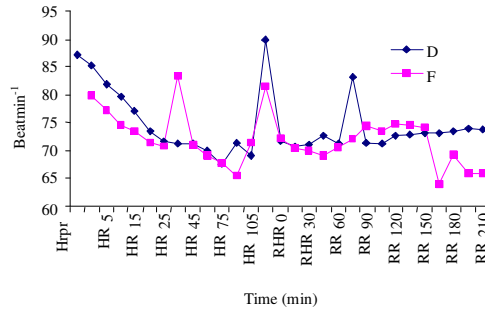| Side Effect	Group D (n= 38)	Group F (n= 38)	P value
Nausea/ Vomiting	2 (5)	4 (10)	0.401
Pruritus	0	5 (13)	0.169
Hypotension	4 (10)	9 (24)	0.242
Bradycardia	2 (5)	3 (8)	0.649
Need for intraoperative analgesia	3 (8)	2 (5)	0.169
Total	11 (29)	23 (60)	0.021

Fig. 1: Heart rate (HR). Values are the means ± SD
Hrpre = heart rate before spinal block
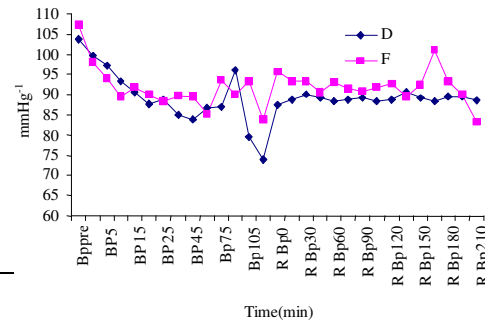R HR = heart rate in the post anesthesia recovery room

Fig. 2: Mean arterial blood pressure (MAP). Values are the means ± SD

Bppre = blood pressure before spinal block
R Bp = mean arterial blood pressure in the post anesthesia recovery room

Hypotension was mild to moderate in both groups except one patient in group F, who had a blood pressure less than 90 mmHg, and required 36 mg ephedrine to restore his blood pressure. Pruritis was absent in group D, but was present in 5 patients in group F, p = 0.169. Nausea and vomiting were more in group F, than group D, but it did not reach statistical difference. Five patients (three in group D, and two in group F), required intraoperative analgesia. Two patients in group F complained of postdural puncture headache which was treated by hydration and simple analgesia.

DISCUSSION

Present results in this study showed that the supplementation of spinal bupivacaine with 5 µg DXM significantly prolonged both sensory and motor block compared with intrathecal 25µg fentanyl and bupivacaine in vaginal reconstructive surgery.

Both fentanyl and DXM improved the quality of intraoperative analgesia and diminished the risk of supplementation of general anesthesia. Fentanyl is a lipophillic µ-receptors agonist opioid. Intrathecally, fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supra spinal spread and action[9,10]. Pain is frequently encountered during surgery on the female genital organs under spinal local anesthetics, intrathecal fentanyl when added to spinal local anesthetics reduces significantly visceral and somatic pain and this analgesic effect has been proved by many studies[11-14].

Intrathecal fentanyl prolongs the duration of spinal anesthesia produced by bupivacaine and lignocaine and this effect has been shown in obstetric and non-obstetric patients undergoing various surgeries[15,16]. The prolongation of the duration of spinal analgesia produced by intrathecal fentanyl is not a dose related. Seewal *et al*.[3] found a significant improvement in the duration and quality of analgesia produced by intrathecal fentanyl and bupivacaine compared to

intrathecal bupivacaine alone, meanwhile, the author found no further increase in the duration of analgesia when the dose of fentanyl was increased from 10 µg to 20, 30, or 40 µg. Kuusniemi *et al.*[15] reported that different durations of spinal anesthesia were related to different doses of spinal bupivacaine supplemented with 25 µg fentanyl in patients undergoing urology procedures. Hamber *et al.*[17] in a review article found that a dose of 20-30 µg fentanyl as adjunct to spinal anesthesia produces faster block onset time, improved intraoperative analgesia and decrease incidence of intraoperative nausea and vomiting in obstetric patients. In non obstetric patients studies demonstrated that adose of 25 µg fentanyl for supplementation of spinal anesthesia produces the excellent quality of perioperative analgesia[18-20]. In present study and based on the above studies findings, fentanyl in a dose of 25 µg was used for supplementation of spinal bupivacaine. DXM is a highly selective α2-adrenoreceptor agonist approved as intravenous sedative and adjuvant to anesthesia. DXM when used intravenously during anesthesia reduces opioid and inhalational anesthetics requirements[21,22]. Compared with clonidine a α2-adrenoreceptor agonist, the affinity of DXM to α2 receptors has been reported to be 10 times more than clonidine[23], moreover, Kalso *et al.*[5] and Post *et al.*[24] reported a 1:10 dose ratio between intrathecal DXM and clonidine in animals. Clinical studies in surgical patients showed that intrathecal clonidine increases the duration of sensory and motor spinal block when added to spinal local anesthetics and this effect of clonidine is dose-dependent[25-27], and doses of more than 75 µg intrathecal clonidine is accompanied by excessive sedation, hypotension and bradycardia. De kock *et al.*[28] recommended a dose of 15-45 µg clonidine for supplementation of spinal anesthesia since this dose effectively prolongs the duration of spinal block with minimal sedation and side effects. The clinical studies about the use of intrathecal DXM in surgical patients are scarce in the literature. Kanazi *et al.*[7] found that 3µg DXM or 30 µg clonidine added to 13 mg spinal bupivacaine produced the same duration of sensory and motor block with minimal side effects in urologic surgical patients. From Kanazi study and animal studies, we assumed that 3-5 µg DXM would be equipotent to 30-45 µg clonidine when used for supplementation of spinal bupivaciane.

Intrathecal DXM when combined with spinal bupivacaine prolongs the sensory block by depressing the release of C-fibers transmitters and by hyperpolarization of pos-synaptic dorsal horn neurons[29-33]. Motor block prolongation by α2-adrenoreceptor agonists may result from binding these agonists to motor neurons in the dorsal horn of the spinal cord[34,35]. Intrathecal α2-receptor agonists have been found to have antinoniceptive action for both somatic and visceral pain[36,37]. In this study, the intrathecal DXM and bupivacaine block has resulted in significantly less side effects than intrathecal fentanyl bupivacaine block.

The most significant side effects reported about the use of intrathecal α2 adrenoreceptor agonists are bradycardia and hypotension, in present study, these side effects were not significant probably because we used small dose of intrathecal DXM which was confirmed by the findings of Kanazi report. In present study hypotension was more in the fentanyl group than in the DXM group, but it did not reach a significant difference. Meanwhile, hypotension occurred 25-30 min after spinal injection. 2 patients in the DXM group and one patient in fentanyl group had mild episodes of hypotension in the PACU. Pruritus after intrathecal fentanyl is reported to be 40-70% but it was only 13% in present study which can be explained by the fact that pruritus is a benign subjective symptom which is under reporting and usually need no treatment.

CONCLUSION

Intrathecal DXM supplementation of spinal block seems to be a good alternative to intrathecal fentanyl since it produces prolonged sensory block, and it is evident that this type of block may be more suitable for major surgeries on the abdomen and lower extremities. The dose of DXM (5 µg) used in present study was suitable and comparable to clonidine 45 µg as suggested by De kock *et al.*[28]. Intrathecal dose of DXM use in present study needs further clinical studies to prove its efficacy and safety and to be considered the suitable dose of DXM for supplementation of spinal local anesthetics. A drawback of DXM supplemented spinal block characteristics in this study is the increase in the duration of motor block which may not suit short term surgical procedures or ambulatory surgery.

In conclusion, 5 µg DXM seems to be an attractive alternative as adjuvant to spinal bupivacaine in surgical procedures especially in those that need quite long time with minimal side effects and excellent quality of spinal analgesia.

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