A COMPARISON BETWEEN THE EFFECT OF ADDING DEXMEDETOMIDINE AND MIDAZOLAM TO INTRATHECAL BUPIVACAINE ON THE QUALITY OF SPINAL BLOCK FOR ORTHOPEDIC SURGERY.

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ABSTRACT

Back ground: In spinal anesthesia various additive drugs have been tried with 0.5%hyper baric bupivacaine to look for the improvement in the quality and the duration of blockade like midazolam & 2-agonists. We designed a prospective, randomized, double blind study to compare the efficacy of midazolam and dexmedetomidine with 0.5% hyperbaric bupivacaine when given intrathecally in terms of effect and maximum level of sensory and motor blockade, overall duration and quality of analgesia, hemodynamic effects during intraoperative periods and any side effects.

Aim of the study: A comparison between the effect of adding dexmedetomidine and midazolam as adjuvant to intrathecal Bupivicaine on the quality of spinal block for orthopedic surgery

Patients and Methods: Sixty six of American Society of Anesthesiologists physical status classes I and II patients scheduled for lower limb orthopedic surgery were enrolled in this study. According to the received intrathecal drug mixture, these patients were randomly divided into 3 equal groups (22 in each group). Group I (control group) received 2.5 ml heavy bupivacaine (0.5%) plus 0.5 ml normal saline intrathecally. Group II (dexamedetomedine group) received 2.5 ml heavy bupivacaine (0.5%) plus 5 µg dexamedetomedine in 0.5 ml normal saline intrathecally. Group III (midazolam group) received 2.5 ml heavy bupivacaine (0.5%) plus 2 mg midazolam in 0.5 ml normal saline intrathecally.

Results: Patients in group II (Dexmedetomidine group) had a significantly longer sensory and motor block time than patients in group III (Midazolam group). The time of sensory block regression to S1 in group II (248.8±32.4 min) was significantly longer than the time in and in group III (208.3±21.7 min) (*P*=0.000). The time of motor block regression to reach Bromage score 0 in group II (235.6±32.4 min) was significantly longer than the time in group III (191.4±14.8 min) (*P*=0.000).

Conclusions: Although both dexmedetomidine (5µg) and midazolam (2mg), when added to intrathecal heavy bupivacaine lead to prolongation of the motor and sensory block with hemodynamic stability and lack of sedation but dexmedetomidine was superior to midazolam in prolongation of the motor and sensory block.

INTRODUCTION

Spinal block is commonly employed for orthopedic surgery. [(1)] It is very economical and easily to administer. However, postoperative pain control is a major problem because spinal anesthesia using only local anesthetics is associated with relatively short duration of action, and thus early analgesics intervention is needed in the postoperative period. [(2)] A common problem during lower abdominal surgeries under spinal anesthesia is visceral pain, nausea, and vomiting. [(3)] Various adjuncts have been used to prolong spinal anesthesia & prolong the analgesic effect of bupivicaine, with the possible advantage of delayed-onset postoperative pain & reduced analgesic requirements. [(4)]

Alpha 2-adrenoreceptor agonists are being increasingly used in critical care and anesthesia. Beside sedation and analgesia, they also decrease sympathetic tone and attenuate the stress response to anesthesia and surgery. In addition, they used as adjuvant drugs during regional and general anesthesia. [(5)] Dexmedetomidine, a new highly selective alpha2 agonist, is under evaluation as a neuraxial adjuvant as it provides stable hemodynamic conditions, good quality of Intraoperative and prolonged postoperative analgesia with minimal side effects. [(6)], also subarachnoid administration of dexmedetomidine has been shown to significantly increase the duration of anesthesia produced by isobaric or hyperbaric bupivicaine with good safety profile. [(1)]

Midazolam is known to produce antinociception and potentiate the effect of local anesthetic when given in neuraxial block, without having significant side effects. [(7)] Intrathecal midazolam has been shown to have analgesic properties and potentiate the effects of intrathecal local anesthetics. The mechanism by which midazolam provide analgesia has been explored in several recent studies, some of which suggest that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal delta receptors. [(8)] The aim of this study was a comparison between the effect of adding dexmedetomidine and midazolam as adjuvant to

intrathecal Bupivicaine on the quality of spinal block for orthopedic surgery.

PATIENTS AND METHODS

This prospective randomized double blind placebo controlled clinical trial was conducted at Zagazig University Hospital, between January 2013 and January 2014, after approval of the hospital ethical committee and written informed consent was obtained from each patient.

This study was carried upon 66 ASA PS class I&II of both sexes adult patients who were scheduled for lower limb elective orthopedic surgery. Exclusion criteria were ASA physical status class III or IV, age less than 18 or more than 50 years, body weight more than 120 kg, height less than 150 cm, patients using alpha 2 receptor antagonists, calcium channel blocker and angiotensin converting enzyme inhibitors, dysrthymia by ECG, contraindication to spinal anesthesia (coagulation disorder, infection at puncture site, increased intracranial tension & hypotension, the use of any opioid or sedative in the week prior to surgery and history of alcohol or drug abuse. Sixty six patients meet inclusion criteria were enrolled in this study. According to the received intrathecal drug mixture, these patients were randomly divided into 3 equal groups (22 in each group). Group I (control group) received 2.5 ml heavy bupivacaine (0.5%) plus 0.5 ml normal saline intrathecally. Group II (dexamedetomedine group) received 2.5 ml heavy bupivacaine (0.5%) plus 5 µg dexamedetomedine (Precedex 100 µg/ml; Hospira, Inc free preservative) in 0.5 ml normal saline intrathecally. Group III (midazolam group) received 2.5 ml heavy bupivacaine (0.5%) plus 2 mg midazolam (Dormicum 5mg/ml; Roche products free preservative) in 0.5 ml normal saline intrathecally. Sedatives were not given as premedication to all studied patients.

On arrival in the operating room, routine monitors were applied for recording ECG, heart rate (HR), mean arterial blood pressure (MAP), and SpO2 values. An intravenous 18G cannula inserted in peripheral vein of the upper limb on which blood pressure cuff was not applied. The patients were preloaded with 15 ml/kg Lactated ringer's solution. 25G spinal needles were introduced through L3-L4 interspaces in sitting position using aseptic precautions. Immediately after local anesthetic mixture injection, patients were made to lie supine.

Heart rate (bpm) and mean arterial blood pressure (MAP) (mmHg) were recorded at 0 (pre-block) then at 5, 10, 20 and 40 min. after spinal block. SpO2 was recorded at 0 (pre-block) then 15, 30, 45 and 60 min. after spinal block. Oxygen (2 L/min) was administrated via a mask if SpO2 decreased below 90%.

Sensory dermatomal block level was detected by loss of pinprick sensation to 23G hypodermic needle on each side mid thoracic line every 2 min until T10 (at which surgery was allowed) and the highest level were achieved then every 10 minute until the point of two segments sensory block regression was observed and then at 30-minute intervals until sensory block regression to S1 was observed. Time to T10 sensory block (min), the achieved highest sensory block level, time to highest sensory block level (min), time to 2 segments regression (min) and time to sensory regression to S1 level (min) were recorded.

Motor block level was assessed according to the Modified Bromage scale (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 the hip and knee, but is able to move the ankle; 3= the patient is unable to move the hip, knee and ankle).[9]

Time to progression of motor block to Bromage score 3 and times to regression of motor block to Bromage score 0 were recorded in each group.

Sedation was assessed by a modified Ramsay sedation scale (1= anxious, agitated, restless; 2= cooperative, oriented, tranquil; 3= responds to commands only; 4= brick response to light or loud noise; 5= sluggish response to light or loud noise; 6= no response). [10] The maximal sedation score was recorded in each group.

Postoperatively, the pain severity score was recorded by using Visual analog pain scale (VAS) between 0 and 10 (0= no pain; 10= most severe pain), initially every 1 hour for 2 hour, then every 2 hour for the next 8 hour and then after every 4 hour till 24 hours. Diclofenac (75mg/3ml) was given intramuscularly as rescue to analgesia when **VAS ≥ 3 and** repeated after 12 hours if needed. Additional breakthrough meperidine was given intramuscularly at 50 mg dosages each time, if necessary.

Time to first analgesic request, Diclofenac consumption (75mg) and the number of patients who needed additional breakthrough meperidine in each group were recorded.

The associated side effects as nausea, vomiting, hypotension, bradycardia, respiratory depression, shivering, pruritus and sedation were recorded. Hypotension was considered if systolic blood pressure decreased by more than 30% from baseline or a fall below 90 mmHg. It was treated with 5mg incremental iv doses of ephedrine & IV

fluid as required. Bradycardia, defined as heart rate <60 bpm, was treated with atropine 0.3-0.6 mg iv.

Statistical analysis was done using the Statistical Package for Social Science (SPSS version 15 for Windows, SPSS Inc, Chicago, IL, USA). To calculate the sample size, a power analysis of β-error=0.8 and α-error= 0.05, showed that 22 patients per study group were needed. Data are expressed as either mean and standard deviation (SD) or numbers and percentages. The normality distribution of the variables was tested using the Kolmogorov-Smirnov Test. Categorical data were analyzed using the chi-square test. The Mann Whitney U-test was used to analyze difference between the groups in pairs if data were not normally distributed while the Student t test was used if data were normally distributed. *P1* denote *P* value of test between 1st group & 2nd group, *P2* denote *P* value of test between 1st group & 3rd group and *P3* denote *P* value of test between 2nd group & 3rd group. As we determine significance of difference between two groups in two directions so two tailed test was used & *P* value < 0.05 were considered to indicate statistical significance.

RESULTS

Statistically, the demographic data and duration of surgery of the three studied groups were comparable (Table 1).

Table (1): Demographic data and duration of surgery in the studied groups.

	Group I (*n*=22)	Group II (*n*=22)	Group III (*n*=22)	P1	P2	P3
Sex (M / F)	12/10	16/6	18/4	0.210	0.052	0.472
Age (years)	30.4 ±8.47	30.36±8.11	31 ± 9.29	0.953	0.962	1.000
Weight (Kg)	81.77±11.83	82.55±9.86	82.62±10.35	0.944	0.981	0.888
Height (cm)	171.36±7.56	170.59±8.48	171.86±8.59	0.757	0.962	0.748
ASA PS Calss 1/II.	15/7	16/6	13/9	0.741	0.531	0.340
Duration of surgery (min).	75.2±10.8	76.8±10.7	76.3±10.9	0.625	0.748	0.868

Data are expressed by numbers and mean ± SD.
n=Total number of patients in each group.
P value >0.05 means non significant differences.

Statistically, heart rate, MAP and SpO2 mean values at various times of measurements of the studied groups were comparable (Table 2, Figure 1, 2 and 3).

Table (2) Heart rate, Mean arterial blood pressure and SpO2 at various times of measurements of the studied groups.

	Group I (*n*=22)	Group II (*n*=22)	Group III (*n*=22)	P1	P2	P3
Heart rate (bpm):						
0 (Pre-block).	86.77±9.97	86.53±8.61	85.77±9.21	0.718	0.713	0.987
After block:	90.45±10.56	89.77±8.64	90.41±8.55	0.816	0.988	0.807
5 min						
10 min	95.86±11.40	80.36±18.49	94.32±6.72	0.002*	0.588	0.003*
20 min	90.0±9.87	89.0±8.18	90.59±6.78	0.743	0.818	0.517
40 min	85.45±8.43	90.69±6.60	85.23±8.65	0.047	0.930	0.042
MAP (mmHg):						
0 (Pre-block)	95±7.09	95.59±7.46	95.05±7.58	0.809	0.923	0.913
After block:	94.77±6.26	94.14±6.67	94.76±6.97	0.800	0.779	0.593
5 min						
10 min	86.68±7.58	87.05±7.93	87.19±7.76	0.797	0.903	0.913
20 min	94.68±6.39	94.5±6.72	93.86±6.12	0.744	0.564	0.783
40 min	95.32±6.77	95.14±7.08	95.05±6.98	0.904	0.981	0.933
SpO2 (%):						
0 (Pre-block)	98.32±1.39	98.77±0.92	98.57±0.92	0.365	0.835	0.414
After block:	97.86±1.49	98.0±1.95	98.0±2.14	0.453	0.396	0.951
15 min.						
30 min.	98.0±1.06	98.09±1.5	97.86±1.82	0.505	0.814	0.614
45 min.	98.36±0.79	98.36±1.0	98.24±1.26	0.871	0.980	0.853
60 min.	98.59±0.85	98.55±0.8	98.43±0.92	0.880	0.542	0.643

Data are expressed by mean ± SD.
n=Total number of patients in each group.
P value >0.05 means non significant differences.

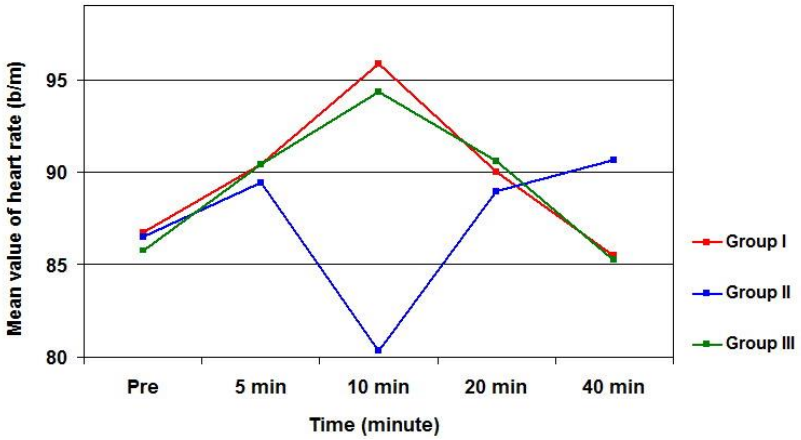

Figure (1) Mean values of heart rate (bpm) at various times of measurements of the studied groups.

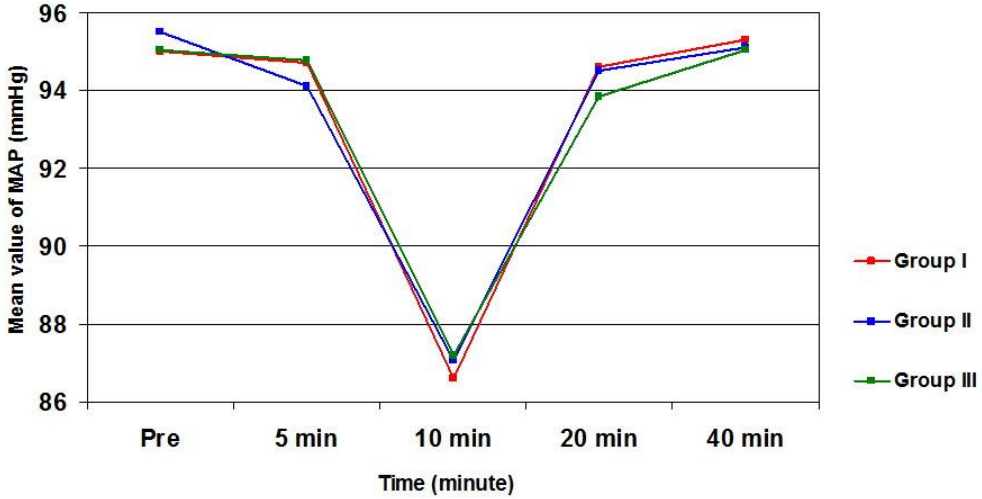

Figure (2) Mean values of MAP (mmHg) at various times of measurements of the studied groups.

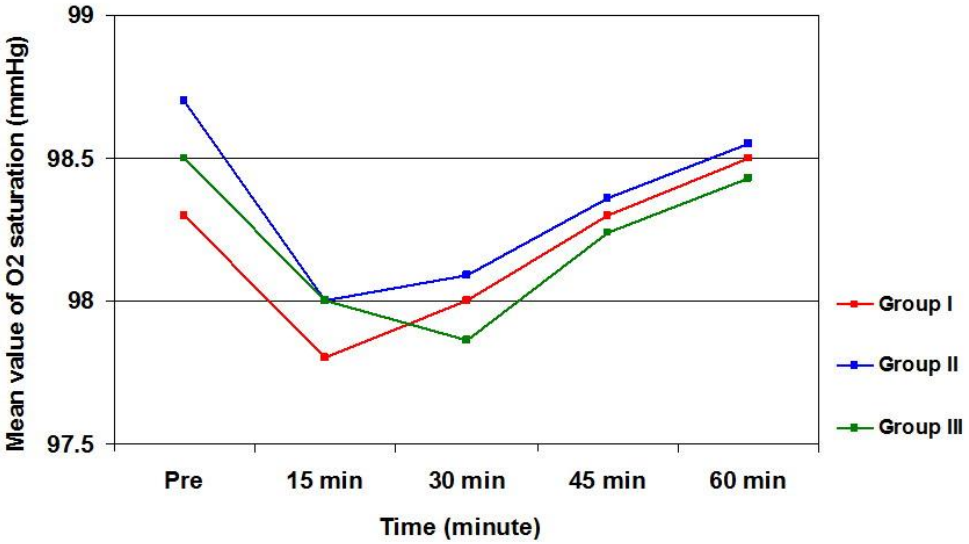

Figure (3) Mean values of SpO2 (%) at various times of measurements of the studied groups.

Statistically, time to reach sensory block T10 level and time to two segment regression of the 3 studied groups were comparable. Times to sensory regression to S1 in group II (248.8±32.4) and III (208.3±21.7) were significantly longer than in group I (162.5±10.3) but this time in group II was significantly longer than in group III (Table 3).

The achieved highest sensory block levels were T6, T5 and T6 respectively in group I, II and III. Statistically, achieved highest sensory block level higher in group II than group I and - group III.

Statistically, time to the achieved highest sensory block level - was 13.7+ 1.7min., 11.7+1.7min. And 12.1+1.6min. in group I, II and III respectively.

Statistically, time to progression of motor block to Bromage score 3 of the three studied groups were comparable (table 3). Times to regression of motor block to Bromage score 0 in group II (235.6±32.4 min.) and group III (191.4±14.8 min.) were significantly longer than in group I (161.3±7 min.) but this time in group II was significantly longer than in group III (Table 3).

Table (3) Anesthesia parameters

	Group I (*n*=22)	**Group II (*n*=22)**	**Group III (*n*=22)**	**P1**	**P2**	**P3**
Time to reach T10 (hr)	9.32±1.52	9.0±1.06	9.24±0.76	0.476	0.980	0.359
The achieved highest sensory block level.	T6(T4-T7)	T5(T4-T8)	T6(T4-T7)	0.448	0.951	0.315
Time to the achieved highest sensory block level (min.).	13.7± 1.7	11.7±1.7	12.1±1.6	0.0180	0.220	0.369
Time to 2 segment regression (min)	93.9±11.2	100.0±11.2	97.38±6.24	0.075	0.250	0.348
Time to sensory regression to S1 (min)	162.5±10.3	248.8±32.4	208.3±21.7	0.000*	0.000*	0.000*
Time to achieve Bromage score 3 (min).	9.09±1.01	8.36±1.49	8.62±1.59	0.117	0.320	0.639
Time to Bromage score **0 (min).**	161.3±7.4	235.6±32.4	191.4±14.8	0.000*	0.000*	0.000*

Data are expressed by mean ± SD, numbers (%) and Median (range)
n=Total number of patients in each group.
* means significant difference (P value < 0.05).
P value >0.05 means non significant differences.

VAS pain scores mean values at various times of measurements of the 3 studied groups were comparable.

Statistically, Diclofenac consumptions in the 3 studied groups were comparable. 13 (59%) patient in group I and no patient in the other 2 groups had received mepridine. Statistically, the number (59%) of patients who received mepridine in group I was significantly higher in comparison to the other 2 groups (Table 5).

Table (5) VAS & analgesia use

	Group I (*n*=22)	Group II (*n*=22)	Group III (*n*=22)	P1	P2	P3
VAS	1.27±0.45	1.5±0.51	1.48±0.51	0.126	0.126	1.000
Preoperative	1.64±0.72	1.5±0.51	2.05±0.8	0.664	0.081	0.047
1hr	2.55±1.14	2.0±0.69	2.05±0.74	0.104	0.132	0.947
2hr	2.73±0.98	2.32±0.47	2.48±0.81	0.275	0.591	0.617
4hr	2.50±0.80	2.36±0.65	3.0±1.0	0.547	0.114	0.036
6hr	4.68±0.89	4.09±0.97	4.24±0.88	0.105	0.203	0.668
8hr	2.64±0.95	2.82±1.0	3.43±0.92	0.536	0.060	0.046
12hr	2.77±0.75	2.41±0.59	2.52±0.75	0.092	0.182	0.825
16hr	2.41±0.66	2.23±0.52	2.43±0.81	0.299	0.696	0.582
20hr	1.27±0.45	1.5±0.51	1.48±0.51	0.126	0.126	1.000
24hr	1.29+0.55	1.5+ 0.62	1.49+0.69	.0129	0.131	1.0140
Time to the first analgesic request minutes	142.5±10.3	228.8±32.4	188.3±21.7	0.000*	0.000*	0.000*
Diclofenac consumption (mg).	65.14± 8.34	0 (0%)	0 (0%)	0.000*	0.000*	NA
Number of patients who needed additional Mepridine	13 (59%)	0 (0%)	0 (0%)	0.000*	0.000*	NA

Data are expressed by numbers (%).
n=Total number of patients in each group.
* means significant difference (P value < 0.05)
P value >0.05 means non significant differences.
NA = statistical analysis is not applicable.

Nausea and vomiting were detected in 2 patients (9 %) of group I, 1 patient (4.5%) in group II and 2 patients (9%) in group III. Statistically, the incidences of nausea and vomiting of the 3 studied groups were comparable. Bradycardia was detected in 6 patients (27.2%) in group II (dexmedetomidine group) and was not detected in group I and III. Statistically, the incidence of bradycardia in group II was significantly higher than in the other 2 groups.

Sedation scores were 1.5±0.51, 1.82±0.73 and 1.67±0.73 in group I, II and III respectively. Statistically, sedation scores of the three studied groups were comparable (Table 6). Hypotension, respiratory depression, shivering and pruritis were not detected in the three studied groups (Table 5).

Table (5): The incidence of the various side effects in the studied groups.

	Group I (n=22)	Group II (*n*=22)	Group III (*n*=22)	P1	P2	P3
Nausea & vomiting.	2 (9 %)	1(4.5%)	2 (9%)	0.550	1.000	0.550
Hypotension.	0 (0. 0%)	0(0. 0%	0(0. 0%)	NA	NA	NA
Bradycardia.	0(0. 0%)	6(27.2%)	0(0. 0%)	0.008*	NA	0.008*
Resp depression.	0(0. 0%)	0(0. 0%)	0(0. 0%)	NA	NA	NA
Shivering.	0(0. 0%)	0(0. 0%)	0(0. 0%)	NA	NA	NA
Pruritis.	0(0. 0%)	0(0. 0%)	0(0. 0%)	NA	NA	NA
Sedation	1.5±0.51	1.82±0.73	1.67±0.73	0.152	0.664	0.386

Data are expressed by numbers (%).
n=Total number of patients in each group.
* means significant difference (P value < 0.05)
P value >0.05 means non significant differences.
NA = statistical analysis is not applicable.

DISCUSSION

In the present study, the used intrathecal dose of dexmedetomidine was based on previous animal studies. [11] A number of animal studies conducted using intrathecal dexmedetomidine at a dose range of 2.5–100 μg did not report any neurologic deficits with its use. [12-16] Fukushima et al administered 2 μg/kg epidural dexmedetomidine for postoperative analgesia in humans but did not report neurologic deficits. [17]

Small doses of intrathecal dexmedetomidine (3μg) used in combination with bupivacaine in humans have 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.[18] Al-Ghanem et al had studied the effect of addition of 5 μg dexmedetomidine intrathecal to 10 mg isobaric bupivacaine in vaginal hysterectomy and concluded that 5 μg dexmedetomidine produces more prolonged motor and sensory block as compared with 25 μg fentanyl.[6] Al-Mustafa et al studied effect of dexmedetomidine 5 and 10 μg with bupivacaine in urological procedures and found that dexamedetomedine prolongs the duration of spinal anesthesia in a dose-dependent manner.[19] The present study has shown that the addition of 5 μg dexamedetomedine with heavy dose bupivacaine significantly prolongs both sensory and motor block. The mechanism by which intrathecal α2-adrenoceptor agonists prolong the motor and sensory block of local anesthetics is not well known. They act by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons. Their analgesic action is a result of depression of the release of C- fiber transmitters and hyperpolarisation of postsynaptic dorsal horn neurons. [20] Local anesthetic agents act by blocking sodium channels. The prolongation of effect may result from synergism between local anesthetic and α2-adrenoceptor agonist, while the prolongation of the motor block of spinal anesthetics may result from the binding of α 2-adrenoceptor agonists to motor neurons in the dorsal horn. [21] Bharti et al. [22] reported that intrathecal addition of 1 mg of midazolam to bupivacaine significantly increased the duration of sensory and motor blockade (to S2 dermatome). Yegin et al. [23] also demonstrated postoperative analgesic effect of 2 mg of IT midazolam was longer than that of the control group after perianal surgery. Most of the similar studies [22-24] assessed the duration of sensory block by the time from start of the block to the regression to the lower lumbar or perianal area. Midazolam, when applied intrathecally, might gain access to analgesic systems mediated by GABA. Kohno et al.[25] reported that the analgesic effect of IT midazolam is induced by an action on GABAergic transmission in substantia gelatinosa neurons of adult rat spinal cord slices. In other study[26] they reported that the midazolam reduced excitatory synaptic transmission by acting on the gamma-aminobutyric acid type A/benzodiazepine receptor in interneurons, leading to a decrease in the excitability of spinal dorsal horn neurons. The clinical use of intrathecal midazolam in patients needs precautions because there have been several studies with different results about the possible neurotoxicity of intrathecal midazolam in animal. Few animal studies have found histopathological evidence of neurotoxicity in rats and rabbits after the use of intrathecal midazolam.[27-29] Various other histopathological studies in animals [30,31] have shown that IT midazolam does not cause any morphological changes in the spinal cord which are suggestive of midazolam-induced neurotoxicity. Borg and Krijnen [32] also reported that the continuous intrathecal administration of midazolam and clonidine produced almost immediate and nearly complete pain relief without tolerance or side effects.

In our patients, the addition of dexmedetomidine or midazolam to bupivacaine did not cause a significant decrease in the blood pressure intra-operatively. Intrathecal local anesthetics block the sympathetic outflow and reduce the blood pressure. Bradycardia was more in the dexmedetomidine group than in the midazolam group, & it was statistically significant. The α-2 adrenergic agents also have anti-shivering property as observed by Talke et al.[12] We too did not find any incidence of shivering in the three groups. The intraoperative sedative effects of IT midazolam are controversial. Yegin et al.[23] reported that the sedative scales were significantly higher in group received bupivacaine plus 2 mg of midazolam, compared to bupivacaine only group. However, Bharti et al. [22] reported that the sedative scores were comparable in both groups. Our study also show similar result to Bharti et al, with comparable Ramazy sedation score in the three groups

Intrathecal α2-receptor agonists have been found to have antinociceptive action for both somatic and visceral pain. [6] Both dexmedetomidine and midazolam provided good quality intraoperative analgesia and hemodynamic stability. The analgesia was clinically better in both dexmedetomidine group & midazolam group as

compared to control and it was statistically significant

CONCLUSION

Although both dexmedetomidine (5µg) and midazolam (2mg), when added to intrathecal heavy bupivacaine lead to prolongation of the motor and sensory block with hemodynamic stability and lack of sedation but dexmedetomidine was superior to midazolam in prolongation of the motor and sensory block.

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