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Research article

Intrathecal dexmedetomidine in TURP operations: A randomised controlled study

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1. Introduction

While spinal anesthesia has many advantages, the limited duration of action appears to be one of its downsides. The use of various adjuncts to local anesthetics (LA) prolongs the spinal anesthesia length and reduces the dose of the LA.

Clonidine, a partial α2 - agonist, has been safely used intrathecally along with local anesthetics [1,2].

Dexmedetomidine (Dex) is a centrally acting highly specific α2-agonist, and its α2/α1 selectivity is eight times higher than that of clonidine [3]. The major advantage of this drug is the lack of respiratory depression, pruritus, nausea, and vomiting [3] which are opioid-related side effects. Dexmedetomidine is commonly used as a sedative, preemptive analgesic [4], to decrease postoperative nausea and vomiting (PONV) [5], and to maintain stable hemodynamics in laparoscopic surgeries [6]. It also has been used as an additive to local anesthetics in peripheral nerve block, brachial plexus block [7], subarachnoid anesthesia and caudal anesthesia [8].

Intrathecal Dex (ITD) has been used as an adjuvant to different local anesthetics in humans with various doses ranging from 2.5 to 15 micrograms (μg) [2,3,9–15] resulting in improving the quality of sensory and motor blockade and increasing their duration and decreasing the dose of local anesthetic used.

Two different doses of dexmedetomidine (1.5 and 3 μg) were added to bupivacaine 0.5%, and its effect was examined on the sensory and motor block characteristics, hemodynamic effects, adverse effect profile, and sedation.

2. Methods

We conducted this study in a prospective, randomized, double-blinded manner after approval of the ethical committee of Faculty of Medicine, Cairo University. It included a total of 45 adult male patients scheduled for elective Transurethral resection of the prostate (TURP) operations, using spinal anesthesia. We obtained Written informed consent from all patients.

In this study, we observed the effect of adding two different low doses of dexmedetomidine to bupivacaine for neuraxial anesthesia on onset and regression of sensory and motor block times together with hemodynamic and sedation changes versus bupivacaine alone in patients undergoing TURP operations.

2.1. Sample size

Power analysis was performed using one-way Analysis of Variance (ANOVA) on time to regression of sensory block to S1 because it is the primary outcome variable in the present study. A previous study [9] showed that the mean of the time of regression of sensory block to S1 was about 226 min with a standard deviation of 26 min. Based on the assumption that adding Dexmedetomidine to intrathecal local anesthetic prolongs the duration of sensory block to 356 min, and taking power 0.09 and alpha error 0.05, a minimum sample size of twelve patients was calculated for each group. A total of fifteen patients in each group were included to compensate for possible dropouts.

2.2. Inclusion criteria

Male gender, age between 50 and 70 years old and Patients' physical status by the American Society of Anesthesiologist (ASA): ASA class I, II and III.

2.3. Exclusion criteria

Contraindications of spinal anesthesia, Patients who were taking α2-adrenergic agonist or antagonist therapy, Patients who were having labile hypertension, uncontrolled cardiac disease, heart block/dysrhythmia, autoimmune disorders, Communication difficulties, e.g. mental retardation or deafness and Allergy to the drug or local anesthetics.

2.4. Premedication and preoperative preparation

No pharmacological premedication was given to the patients.

2.5. Study procedures

Standard monitoring including electrocardiogram (ECG), pulse oximetry (SpO2) and noninvasive blood pressure (NIBP) was attached to the patients upon their arrival to the operating room.

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Baseline parameters were recorded, and monitoring was initiated. Intravenous (IV) access was secured using 18G cannula. Resuscitation equipment such as appropriate sizes of tracheal tubes, laryngoscopes with long and short blades, an oxygen source, vasopressors and resuscitation bag were prepared for any possible intervention. 10–20 ml/kg of lactated Ringer was given as a preload. The patients were supported to be in the sitting position for preparation for the administration of the local anesthetic. Complete aseptic precautions including cleaning with povidone iodine and draping were performed. The L3/L4 or L4/L5 intervertebral space was located. The skin overlying the intervertebral space identified was anesthetized with 3 ml of 2% lidocaine using a size 22G hypodermic needle. Lumbar puncture was performed using a 23 or 25G pencil point spinal needle to inject the study agent intrathecally. After testing the backflow of cerebrospinal fluid, the intrathecal injectate was given over approximately ten seconds. The spinal needle was then withdrawn, and a light dressing placed over the puncture site.

2.6. Study medication, randomization, blinding and concealment

We used random number table generated by a computer to allocate the study groups. These random numbers were sealed in opaque envelopes and were opened by an anesthesiologist not involved in the intraoperative or postoperative care of the patients.

An anesthetist not involved in the intraoperative management or postoperative assessment prepared the intrathecal injectate under strict aseptic precautions in an unlabeled syringe.

The patient, the surgeon, the in-charge anesthesiologist responsible for the intra-operative care, and the individual who performed the postoperative evaluations were blinded to the patient group assignment.

The following intrathecal injectate was administered according to the patient group assignment with 15 patients included in each group:

- The dose of hyperbaric bupivacaine 0.5 % (Marcaine Spinal, heavy 0.5%, bupivacaine hydrochloride, AstraZeneca) was identical in all groups (15 mg, 3 ml).
- Control group received 15 mg of hyperbaric bupivacaine 0.5% (Marcaine Spinal, heavy 0.5%, bupivacaine hydrochloride, AstraZeneca) + normal saline (0.5 ml).
- Dex 1.5 μg group received 15 mg of hyperbaric bupivacaine 0.5% +1.5 μg Dexmedetomidine (Precedex 100 ug/ml; Hospira, Inc).
- Dex 3 μg group received 15 mg of hyperbaric bupivacaine 0.5% + 3 μg Dexmedetomidine.

All patients received a total volume of 3.5 ml.

Assessment of sensory and motor blocks:

We assessed the sensory level by the loss of pinprick sensation to a short beveled 23G hypodermic needle. Assessment of the dermatomal level was done every 2 min in the mid-clavicular line bilaterally for four consecutive tests. Frequent testing every twenty minutes was performed till recovery of S1 dermatome.

Motor blockade was assessed using the modified Bromage scale [16], (Table 1). Patients were discharged from the postanesthesia care unit (PACU) after sensory regression to S1 dermatome and adequate recovery of their motor power. All the durations were calculated considering the time of spinal injection as time zero. Data regarding the highest dermatome level of sensory blockade, time to T10, time to S1 level sensory regression, degree and duration of the motor block, motor block onset and duration of surgical procedure, were all recorded.

Table 1
Modified Bromage score [16].

Score	Degree of block
0	Free movement of legs and feet
1	Just able to flex knees with free movement of feet
2	Unable to flex knees but with free movement of feet
3	Unable to move legs or feet

2.7. Monitoring and management of intraoperative hemodynamics

Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded every three minutes for the first ten minutes after the block, then every five minutes till the end of the operation, then every fifteen minutes in the post- anesthesia care unit (PACU). Hypotension was defined as a decrease of >20% from baseline, or to <90 mmHg in systolic blood pressure, and was treated with 10 mg intravenous (IV) ephedrine. Bradycardia was defined as heart rate <50 beats/min and was treated with 0.3–0.6 mg IV atropine. Respiratory depression was defined as respiratory rate <10 or SpO2 <95%.

2.8. Assessment of sedation

The level of sedation was evaluated intraoperatively and postoperatively every fifteen minutes using the Ramsay sedation scale [17] (Table 2).

2.9. Primary outcome parameter

The time of sensory regression to S1 dermatome.

2.10. Secondary outcomes parameters

The highest dermatome level, time for the block to reach T10 dermatome, onset to complete motor block time reaching to Bromage 3, motor block regression to Bromage 0 and sedation.

2.11. Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22. Data were summarized using mean and standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between groups were made using ANOVA with post hoc test in normally distributed quantitative variables while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. For comparison of serial measurements within each group repeated measures ANOVA was used in normally distributed quantitative variables while non-parametric Friedman test was used for non-normally distributed quantitative variables. For comparing categorical data, Chi-square test was performed. The exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

Table 2
Modified Ramsay sedation score [17].

Score	Responsiveness
1	Patient is anxious and agitated or restless, or both
2	Patient is cooperative, oriented and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

3. Results

The total number of patients who fulfilled the inclusion criteria was 45. No patients dropped out from the study (Fig. 1). Demographic data were comparable in the three study groups (Table 3).

Dexmedetomidine decreased the heart rate (HR) between the groups as shown in Fig. 2; however, all readings are within the clinically acceptable range.

Figs. 3 and 4 show the readings of systolic and diastolic blood pressure all through the intra-operative period and postoperative period. Dexmedetomidine decreased the mean of the systolic and diastolic blood pressure readings; however, all values were within the clinically acceptable range.

Sensory block characteristics (Table 4) namely; *time to T10* was significantly shorter in Dex 3 μg compared to Dex 1.5 μg and the control group. There was a dose-response prolongation of the time to *sensory block regression to S1 (duration of the sensory block)* between the groups. Also, the *highest level of sensory block* was significantly higher in Dex 3 μg group in comparison to other groups.

Motor block characteristics namely time to *complete regression of motor blockade to Bromage 0* is significantly longer in dex 3 μg compared to the other groups as shown in Table 4. There was no significant difference between the groups regarding the time to reach complete motor block (Bromage 3).

Ramsay sedation score is significantly higher in dex containing groups starting from 30 min as shown in Table 5.

The side effects that were observed in the groups are summarized in Table 6. Some cases of bradycardia and hypotension were observed, but they were not statistically significant.

4. Discussion

Dexmedetomidine is a centrally acting highly specific α2 -agonist and its α2/α1 selectivity is eight times higher than that of clonidine [18].

Dexmedetomidine has activity at a variety of locations throughout the central nervous system. The sedative and anxiolytic effects of dexmedetomidine result primarily from its activity in the locus ceruleous of the brain stem. Stimulation of alpha2-adrenergic receptors at this site reduces central sympathetic output, resulting in increased firing of inhibitory neurons [18–20]. The release of substance P is modulated by the presence of dexmedetomidine at alpha2-adrenergic receptors in the spinal cord (dorsal horn cells) resulting in its analgesic effect. The prolongation of the motor block of spinal anesthetics may be the result of binding of α2 adrenoreceptor agonists to the motor neurons in the dorsal horn [18–20].

Dexmedetomidine used in neuraxial blocks in experimental and clinical studies without neurological deficits has encouraged its use in humans by the intrathecal route with different local anesthetics in a dose ranging from 2.5 μg to 15 μg [2,3,9–15].

The current study compared two low doses of intrathecal Dex; 1.5 μg and 3 μg with a control group. Other studies compared Dex

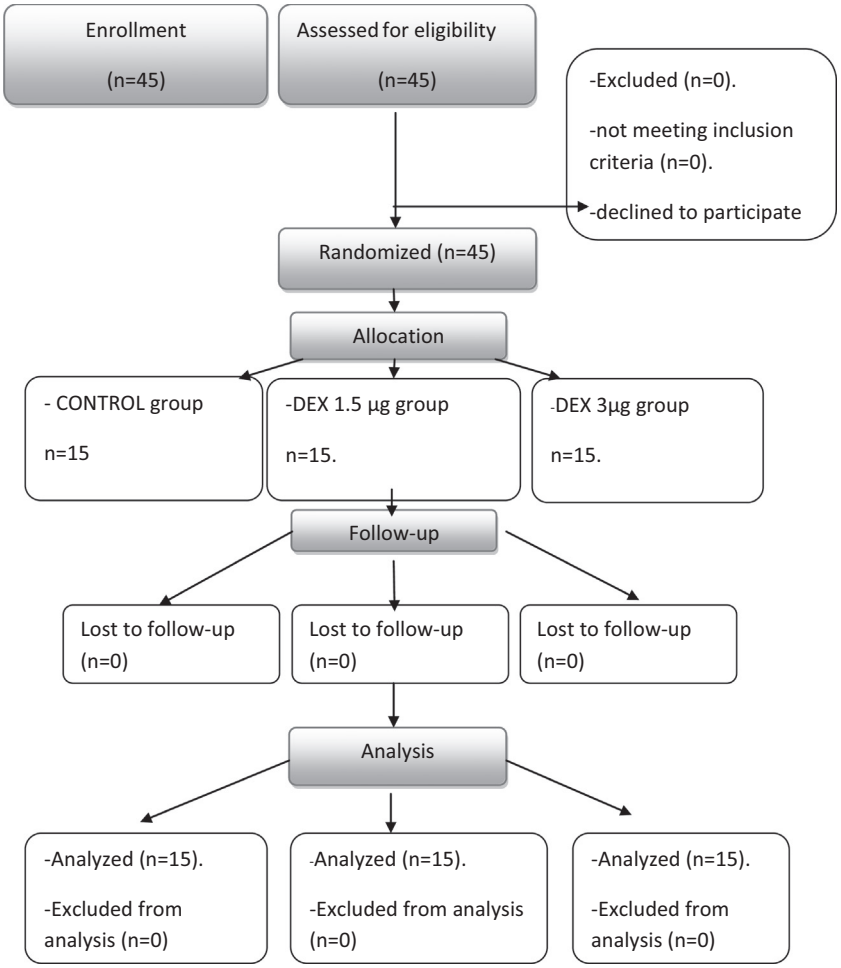

Fig. 1. CONSORT flow diagram showing number of patients at each phase of the study.

Table 3
Demographic data.

	Control (n = 15)	Dex 1.5 μg (n = 15)	Dex 3 μg (n = 15)	P value
Age (years)	66.8(10.2)	62.7 (9.5)	65.3 (7.3)	0.468
Weight (kg)	78.8 (3.7)	75.6 (6.7)	79.4 (7.6)	0.222
Duration of operation (min)	80.1(20.5)	83.5(14.5)	79.3(18.2)	0.793
ASA score (I/II/III)	4/5/6	5/6/4	4/7/4	0.941

Values are means (SD), number (frequency).
ASA: American Society of Anesthesiologist physical status.

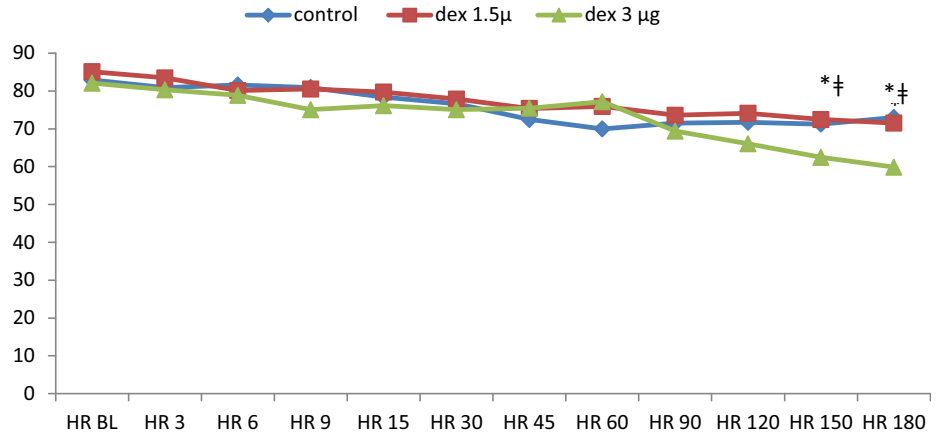

Fig. 2. Heart rate values for the groups; intra-operative and post-operative. * denotes a statistically significant difference in the HR between the control group and dex 3 μg group. ǂ denotes a statistically significant difference in the HR between dex 1.5 μg group and dex 3 μg group.

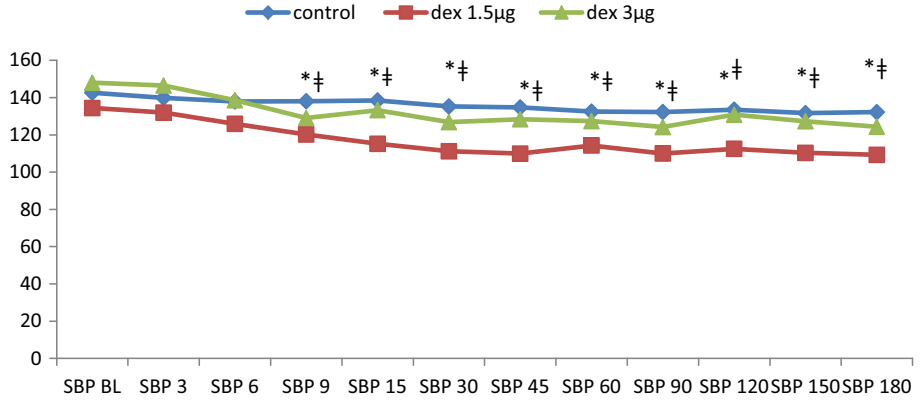

Fig. 3. Systolic blood pressure values for the groups. * denotes a significant statistical difference in SBP between the control group and the dex 1.5 μg group. ǂ denotes a significant statistical difference in SBP between dex 1.5 μg and dex 3 μg groups.

3 μg with saline as the study done by Esmaoglu et al. [9] and Kim et al. [21], or to a much bigger dose of 5 μg by Sudheesh K et al. [22] or to clonidine by Kanzai et al. [2].

It was observed that the duration of sensory and motor blockade increased in this study significantly and congruently with the increase in the dosage of intrathecal Dex. The striking observation in this study is the extremely satisfactory effect of the minuscule dose of intrathecal dex (1.5 μg) used.

Esmaglou et al. [9] did a randomized controlled study on 60 patients undergoing transurethral resection of the prostate. Patients were randomized into two groups; A control group and a Dex 3 μg group added to 15 mg of 0.5% levobupivacaine; they found a statistically significant prolongation of the sensory and motor block duration in the dex containing group ($p < 0.001$). These results are also comparable with Kanzai et al. [2] who compared Dex 3 μg with a control group and with clonidine 30 μg. They noted a significant prolongation of the sensory block duration ($p < 0.001$) in the Dex group in comparison with the clonidine and the control group which goes along with the current study.

Sudheesh et al. [22] compared 3μ to 5μ Dex added to low-dose bupivacaine (4 mg) 0.5% on fifty patients performing ambulatory peri-anal surgeries. They noted an increase in the length of the sensory block and motor block in a dose-dependent manner. The results of Sudheesh et al. [22] were insignificant $p = 0.5$, 0.39 respectively. The results of Sudheesh et al. [22] may be attributed -as mentioned by the author -to the low dose of local anesthesia used and the sitting position for 5 min after administration of the drug which may limit its spread.

Kim et al. and Kanzai et al. [21,2] showed significant prolongation of the time to regression of two sensory dermatomes, $p = 0.002$ and 0.003 respectively.

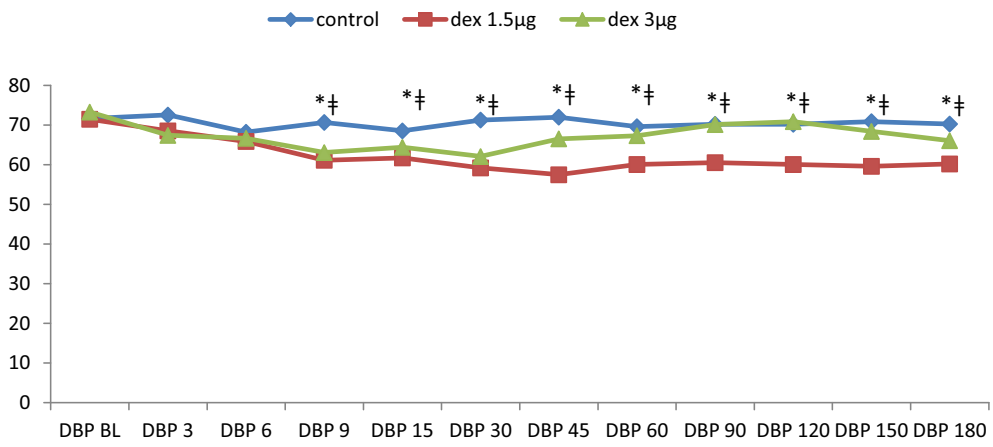

Fig. 4. Diastolic blood pressure values of the groups. * denotes a significant statistical difference in DBP between the control group and the Dex 1.5 μg group. ǂ denotes a significant statistical difference in DBP between Dex 1.5 μg and Dex 3 μg groups.

Table 4
Sensory and motor block characteristics.

	Control (n = 15)	Dex 1.5 μg (n = 15)	Dex 3 μ (n = 15)	P value
Time toT10 dermatome (min)	7.1(2.5)	4.0 (1.5)*	3.2 (1.0)*	<0.001*
Duration of sensory block (min)	128.6 (19.9)	226.6 (52.0)*	301.3 (42.3)*,†	<0.001*
Highest level sensory block (T)	T8(T6-T10)	T6(T4-T8)*	T6 (T4-T8)*	0.011*
Onset of complete motor block (min) (bromage = 3)	8.5 (4.2)	7.4(5.4)	6.9(5.0)	0.660
Duration of motor block (min)	117.3 (24.0)	205.3 (44.3)*	271.3 (35.8)*,†	<0.001*

Values are means (SD).
* Denotes statistical significance compared to the control group.
† Denotes statistical significance compared to dex 1.5 μg.

Table 5
Ramsay sedation score values in different groups.

	Control	Dex 1.5 μg	Dex 3 μg	P value
Baseline	1(1-1)	1(1-1)	1(1-1)	1.00
30 min	1(1-1)	2(1-2)*	2(1-2)*	0.001*
60 min	1(1-1)	2(2-2)*	2(2-2)*	<0.001*
120 min	1(1-1)	2(2-2)*	2(2-2)*	<0.001*
180 min	1(1-1)	2(2-2)*	2(2-2)*	<0.001*

Values are median (interquartile range).
* Denotes statistical significance compared to control group.

Table 6
Adverse effects.

	Control	Dex 1.5 μg	Dex 3 μg	P value
Bradycardia	2 (13.3%)	4 (26.7%)	5 (33.3%)	0.566
Hypotension	3 (20.0%)	3 (20.0%)	2 (13.3%)	1
Nausea	1 (6.6%)	2 (13.3%)	1 (6.6%)	1
Vomiting	0 (0%)	1 (6.6%)	1 (6.6%)	1

Values are count (percentage).

Time to T10 dermatome was significantly shorter between the groups ($p < 0.001$) in the current study, whereas Esmaoglu et al. [9] and Kanzai et al. [2] found it non-significant.

In this trial, we observed that Dex increased the highest level of the block significantly ($p = 0.011$), in contrast to other studies which didn't find a significant difference [2,9,21].

The duration of motor block onset time was shorter in Dex containing groups but insignificantly, whereas Esmaoglu et al. [9] noticed a significant decrease in time ($p < 0.001$).

Yektas et al. [23] compared the effect of adding 2 μg and 4 μg dex to 15 mg of bupivacaine 0.5% on 60 male patients undergoing an inguinal hernia operation; they also found a statistically significant dose- dependent prolongation of sensory and motor block times between the groups ($p < 0.001$).

Gupta et al. [15] compared three doses of dexmedetomidine (Dex 2.5 μg, 5 μg and 10 μg); in addition to 3 ml of bupivacaine 0.5%, randomized into three groups (n = 30) on patients undergoing elective lower abdominal and lower limb procedures. In addition to measurement of sensory and motor block characteristics which goes along with other studies [2,9,13,21,22] they measured differential analgesia (DA is defined as the time difference from the end of the motor blockade to the first analgesic requirement). They found that Increasing the dosage of intrathecal dexmedetomidine (ITD) from 2.5 μg to 10 μg resulted in a 41.28%, 67.28% and 208.37% increase in the duration of the motor block, analgesia, and DA, respectively. A long period of DA has the advantage of minimizing the complications of postoperative pain (delayed wound healing, prolonged hospitalization, the risk of neuro-sensitization, and hence, chronic pain) as well as that of prolonged motor blockade (reduced mobilization, deep venous thrombosis, and pulmonary embolism).

As regards to hemodynamics, this study goes along with other studies [2,9,13,15,21,22] showing comparable mean values of heart rate readings between the three groups. Regarding blood pressure readings, we found that there was a statistically significant difference between the groups, but they were all within the clinically accepted range; in contrast to other studies which observed comparable mean arterial pressure values between the groups [9,13,15].

When we measured the percentage degree of decrease in blood pressure within in each group, we found that the reduction in the mean of systolic blood pressure in the Dex 1.5 group was 18% and that of the Dex 3 group was 16%.

Therefore, the two doses of Dex decreased blood pressure to almost the same extent. The mean of the baseline reading of systolic blood pressure in the Dex 1.5 group was lower (134.4) than the Dex 3 group (1 4 8); this may be an explanation of the lower readings in the Dex 1.5 group.

Hemodynamic instability namely bradycardia and hypotension are the most common side effect noted with the use of α2 agonists [15].

In the current study; we observed 4 cases of bradycardia in Dex 1.5 μg group versus 5 cases in Dex 3 μg group, But they were clinically insignificant. This goes along with most clinical studies [2,9,21,22]. On the other hand, Bindra et al. [24] reported the occurrence of severe bradycardia followed by sinus arrest in a 40- year-old woman scheduled for total hysterectomy 70 min after receiving intrathecal bupivacaine 0.5% 2.5 ml plus dexmedetomidine 10 μg. The level of sensory block was at T_{10} at this time. She became vitally stable after receiving three doses of atropine [24].

Halder et al. [25] noticed statistically significant occurrence of bradycardia ($p < 0.05$) in the Dex groups in a randomized controlled trial performed on Eighty patients scheduled for elective lower limb surgeries.

Other adverse effects namely hypotension, nausea, and vomiting were comparable between the groups and went along with the results of other clinical studies [2,9,15,22]. On the other hand Yektas et al. [23] noted clinically significant difference ($p = 0.002$) between the groups regarding hypotension.

Dex produced a dose-dependent sedative effect between the groups ($p < 0.001$) in the present study which was supported by other studies [13,15,23]. On the other hand, Sudheesh et al. [22] didn't find a significant difference between the groups; their result was supported by Kanzai et al. [2] where their sedation score lies in the range of 0–1 for all patients.

Several studies used bigger doses of intrathecal dexmedetomidine. Al Mustafa et al. [13] compared the effect of adding 5 μg and 10 μg of dexmedetomidine to intrathecal bupivacaine on block characteristics on 66 patients. They found that Dex has a dose-dependent effect on the onset and regression of sensory and motor block, with statistically significant difference between the groups ($p < 0.001$). Hala et al. [12] did another study where they used much bigger doses of intrathecal dex (10 and 15 μg). They noted dose-dependent prolongation of sensory and motor block duration.

A large meta-analysis [26] including 1092 patients from 16 RCT was performed to assess the effect of different doses of intrathecal dex (spinal and epidural) on postoperative pain intensity, duration of analgesia, bradycardia and hypotension as a primary outcome. In addition to sensory and motor block characteristics and 24-h postoperative sedation as secondary outcomes.

They noted that Dex significantly decreased postoperative pain intensity, increased analgesic duration and increased the incidence of bradycardia. On the other hand, there was no significant increase in the incidence of hypotension in comparison with the placebo group. Also, the onset of the sensory block was significantly shortened in addition to increased sensory and motor duration and postoperative sedation scores. On the other hand, Dex didn't affect the onset of motor block.

Another meta-analysis was done by Abdalla et al. [27] where they included 516 patients from 9 different RCT; 5 of which are spinal anesthesia and the remaining 4 are brachial plexus block. They assessed the effect of dex as a LA adjunct on block characteristics and side effect profile. They observed that intrathecal Dex significantly prolonged sensory duration, motor duration and length of analgesia with an increase in the incidence of bradycardia by 7%. On the contrary, perineural Dex failed to show significant prolongation in the sensory duration.

5. Limitations

Although our study added to the general knowledge of intrathecal dexmedetomidine; we must regard some limitations. This study lacks long postoperative follow-up to detect any potential neurological complications. We used 15 mg of hyperbaric bupivacaine; further studies are needed to be done using intrathecal Dex as an adjuvant to lower doses and different types of local anesthetic.

6. Conclusion

Dexmedetomidine is a favorable adjunct when applied intrathecally. It prolongs motor and sensory block time significantly; improves its quality and the need to sedatives; our recommendation is to start using it in a small dose (1.5 μg) especially in short operations and elderly population due to its favorable effects regarding the duration of anesthesia and sedation.

Conflict of interest

The authors have no conflict of interest with this work.

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