

Comparison of 3 Different Dexmedetomidine Doses and Their Effect on the Duration of Spinal Anesthesia

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Abstract

Background and aim: Dexmedetomidine has been tested in many studies as an adjuvant to prolong spinal anesthesia duration with no clear recommendation regarding the optimum dose. This study test very minimal dose of Dexmedetomidine 1.5 µg vs. 3 µg and 5 µg to find out the least effective dose.

Methods: 94 patients were recruited and randomly divided into 4 groups C, D1.5, D3 and D5 received saline, 1.5 µg, 3 µg and 5 µg Dexmedetomidine respectively in combination with the levobupivacaine through intrathecal route. Duration of the spinal anesthesia, sedation score and complications were noticed and recorded in all the groups.

Results: there was an increase in sensory block duration with the increase in dose (dose-related prolongation) as it was 215.9 ± 82.4 min in group C, 219.7 ± 52 min in group D1.5, 301.3 ± 42.3 min in group D3 and 365.4 ± 96.4 min in group D5. However, there was neither statistical nor clinical significance between the control group and group D1.5 (p-value was 0.23). On the other hand, there was neither statistical nor clinical significance regarding the sedation level or the complications.

Conclusions: Dexmedetomidine has an effect on the duration of the spinal anesthesia all through its doses. However, there is no clinical significance with dose 1.5 µg

Keywords: Spinal anesthesia; Dexmedetomidine

Introduction

Nowadays spinal anesthesia has a big role in anesthesia because of its advantages in the form of reducing the metabolic stress, less blood loss, lower incidence of venous thromboembolism, reduction in pulmonary complications, early return of bowel function, shorter admission-discharge interval. However, the limited duration of action is one of its disadvantages. Many studies have tried to increase the spinal anesthesia duration by adding medications *via* intrathecal or intravenous routes, for instance, Intrathecal α_2 -agonists that prolongs the duration of action of local anesthetics and reduce the total required dose [1,2].

One of the most recent and promising α_2 agonists is Dexmedetomidine which is a centrally acting highly specific α_2 -agonist. It shows a α_2/α_1 selectivity 8 times higher than that of Clonidine [3]. It has a sedative effect, pre-emptive analgesia and decrease the incidence of postoperative nausea and vomiting (PONV) [4,5]. Moreover, it shows a hemodynamic stability [6]. Also, it has been used as an adjuvant to local anesthetics in peripheral nerve blocks [7], subarachnoid anesthesia and caudal anesthesia [8].

Different doses of Intrathecal Dexmedetomidine (from 2.5 to 15 µg (µg) has been tried in combination with different local anesthetics in humans to prolong the duration of the spinal anesthesia and to decrease the required local anesthetic doses [2,3,9,10].

In this randomized, controlled, double-blind study, we will examine the effect of different doses of Dexmedetomidine through the intrathecal route from 1.5 µg to 5 µg in combination with levobupivacaine 0.5% aiming at finding the least effective dose of Dexmedetomidine that will prolong the spinal anesthesia duration to a clinical significance with the least side effects. This is the first study to investigate such a small dose of Dexmedetomidine as 1.5 µg.

Methodology

This is a randomized double-blinded controlled trial that was conducted in Cairo university hospital between January 2017 and May 2017 after clinical trial registration number NCT 03143010 and ethical committee approval. All patients who were eligible for the lower half of the body surgery under spinal anesthesia were included in this study after applying legibility criteria, thorough examination, detailed description and signing approval consent.

The inclusion criteria were: any gender between 18 and 70 years with American Society of Anesthesia physical state I or II (ASA I or II) with body mass index (BMI) 40 kg/m² or below (considered obesity with potential difficulty and complications). On the other hand, exclusion criteria were: any gender with age below 18 or above 70 and or BMI more than 40 kg/m², patient refusal, coagulopathy, allergy to the used drugs ASA more than II, obstacles in communications such as mental retardation, dementia, deaf, mute etc. Also, patients that were under treatment with α_2 -adrenergic agonist or transformed to general anesthesia were excluded.

All patients that were included were randomized, using computer generated random number table, to four groups: control group (group C) and three experimental groups (groups D1.5, D3 and D5). All patients were subjected to detailed history, thorough examinations, and full laboratories before the procedure, consent was signed after detailed explanation and finally; patients were included randomly in one of the four groups.

The procedure was double blinded to both the patients and the one who made the follow-up (physician, technician, intern or well-trained nurse). However, it was not blinded to the anesthetist who gave the medications for the aim of safety.

An intravenous (IV) line was inserted and crystalloid solution 15 ml/kg was given to each patient, full monitoring was connected (blood pressure, heart rate (HR), peripheral oxygen saturation (SpO₂) and electrocardiography), baseline data were recorded. The patient was in the sitting position; the back was sterilized by Povidone iodine. The L₃/L₄ or L₄/L₅ intervertebral space was located. 3 mL of 2% lidocaine was infiltrated subcutaneously and into a deeper ligament.

At the site of local anesthesia, a spinal needle 25G was advanced till reaching the intrathecal space and cerebrospinal fluid (CSF) flows through the needle, and then the following were injected according to the groups:

Group C: 3 mL (15 mg) of 0.5% levobupivacaine+0.5 mL normal saline.

Group D1.5: 3 mL (15 mg) of 0.5% levobupivacaine+0.5 mL (1.5 µg) Dexmedetomidine.

Group D3: 3 mL (15 mg) of 0.5% levobupivacaine+0.5 mL (3 µg) Dexmedetomidine.

Group D5: 3 mL (15 mg) of 0.5% levobupivacaine+0.5 mL (5 µg) Dexmedetomidine.

Dexmedetomidine was prepared by dilution on saline to reach the needed dose under complete sterile precautions. For instance; 0.3 ml of Dexmedetomidine with 30 µg was diluted on 100 ml saline to become 3 µg/ml to achieve 1.5 µg per 0.5 ml.

The spinal needle was then withdrawn and a dressing was placed over the puncture site and rapidly the patient was set in the supine position with continuous recording of the vitals every 5 min.

The patients in all the four groups were looked for the following outcomes:

Duration of the spinal sensory blockade (primary outcome), the onset of the blockade, the level of sedation, duration of motor blockade, hemodynamics, complications (hypotension, nausea, vomiting, allergy, any adverse effect specified by the patients). Also, patient's demographic data were collected (age, sex, BMI and duration of surgery).

Duration of the block was considered as the time from solid and stable sensory block to the time of two segment regression using the skin pricks every 5 min, while the onset of the block was considered as the time elapsed from the needle withdrawal to the time with a full sensory block with stationary sensor level.

Sensory block was assessed using a loss of cold sensation every 2 min till having a stable sensory level for the next 20 min.

Motor block was assessed by modified Bromage scale [11] (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).

Sedation was assessed using Ramsay scale [12] 1-patient anxious, agitated or restless scale 2-patient cooperative, oriented and tranquil alert scale 3-patient responds to commands scale 4-asleep but with brisk response to light glabellar tap or loud auditory. Scale 5-asleep, sluggish response to glabellar tap or loud auditory stimulus scale 6-asleep no response.

Hypotension was considered as 20% reduction of the mean arterial pressure from the baseline and was treated by ephedrine increments 9 mg each.

Sample size

Using one-way Analysis of Variance (ANOVA), a Power analysis was performed on time to regression of sensory block as it is the primary outcome variable in the present study. Based on previous studies [10,13-15] showed that the standard deviation of the time of regression of sensory block was about 26 min with a mean 226 min and assuming that 50% prolongation of the sensory block duration more than the control group has a clinical significance and taking power 0.09 and alpha error 0.05, a minimum sample size of twelve patients was calculated for each group raised up to 15 to avoid dropouts.

Statistical analysis

Data were recorded 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 done 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

Results

All patients that were admitted for the lower half of the body surgery under spinal anesthesia during the period from January 2017 to May 2017 in orthopedic theater in Cairo university were assessed for legibility (145 patients) 25 of them were excluded while 120 were asked to share in the study. Only 108 accepted and signed the consent while 12 refused.

Any case that experienced failed spinal anesthesia or converted to general anesthesia for any cause were excluded and considered as a dropout (14 cases in all groups). Fortunately, no cases dropped out because of failure of follow-up (Figure 1).

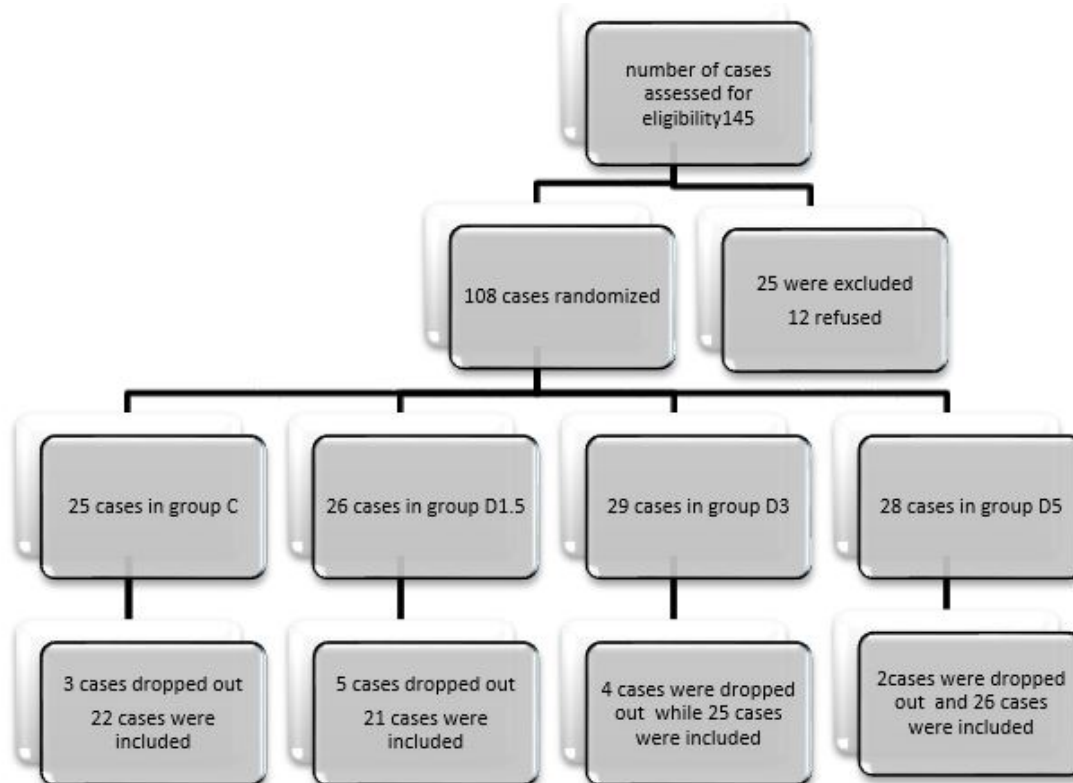


Figure 1: Flow diagram.

Although the sample size calculation for each group was 15, because of the fear of dropouts and the special character of the hospital as a teaching hospital which will subsequently increase the probability of failed spinal or prolonged surgery we included all the legible cases.

Regarding the demographic data and their durations, there were no statistical differences between the groups (Table 1).

	Group C (n=22)	Group D1.5 (n=21)	Group D3 (n=25)	Group D5 (n=26)	P value
Age	40.5 ± 13.4	38.9 ± 11.7	43.8 ± 9.8	42.12 ± 8.97	0.62
Gender (m/F)	16/6	14/7	20/5	18/8	0.24
BMI (Kg/m ²)	27.23 ± 3.25	28.95 ± 3.02	30.3 ± 1.68	29 ± 2.87	0.222
Duration of surgeries (min)	79.2 ± 20.5	82.4 ± 19.4	80.3 ± 21.2	84.02 ± 20.2	0.683
ASA (I/II)	20/2	20/1	18/7	19/8	0.83

Table 1: Demographic and clinical characteristics. Numerical data were presented as Mean ± Slandered deviation (SD), P* value<0.05 was considered statistically significant.

Regarding the onset of the sensory block, there were statistical differences among groups as group C showed onset after 1.4 ± 1.4 min

while group D1.5 showed onset of sensory block after 2.3 ± 1.98 min while in group D3 it was 3.03 ± 2.3 min and in group D5 it was 2.58 ± 3.25 min.

The previous results showed a dose-response prolongation to the Dexmedetomidine; this prolongation shows a statistically significant between the control group C and the other three groups (p-value 0.001). On the other hand, there were no statistical differences among the study groups (p-value 0.61). Moreover, this prolongation has no clinical significance.

Regarding the duration of the sensory block there is, again, a dose-related prolongation with a crescendo pattern (group C 215.9 ± 82.4 min), group D1.5 (219.7 ± 52 min), group D3 (301.3 ± 42.3 min), group D5 (365.4 ± 96.4 min)). However, there was no statistical significance between the control group and group D1.5 (p-value was 0.23). On the contrary, there was a prolongation in both groups D3 and D5 which have achieved a statistical significance (p value was<0.001) in comparison with the control group (Table 2).

The same pattern was achieved in the duration of the motor block as it was (205.3 ± 44.3 min) in group C, (249.3 ± 81.4 min) in group D1.5, (271.3 ± 35.8 min) in group D3 and (319.7 ± 92.2 min) in group D5. The above results showed a statistical difference with significance between groups D5 and D3 on one hand and control group C on the other hand with p-value 0.003. Likewise, there was no statistical significance between both groups C and D1.5 with p-value 0.53 and even more among any experimental groups (D1.5, D3 and D 5 vs. each other) (Table 2).

	Group C (n=22)	Group D1.5 (n=21)	Group D3 (n=25)	Group D5 (n=26)	P value
onset of the sensory block (min)	1.4 ± 1.4	2.3 ± 1.98*	3.03 ± 2.3*	2.58 ± 3.25*	0.001
duration of the sensory block (min)	215.9 ± 82.4	219.7 ± 52 min p value 0.23 vs. C	301.3 ± 42.3 min*	365.4 ± 96.4*	<0.001
duration of the motor block (min)	205.3 ± 44.3	249.3 ± 81.4 p value 0.53 vs. C	271.3 ± 35.8*	319.7 ± 92.2*	0.003

* Denotes statistical significance compared to the control group.

Table 2: Sensory and motor block pattern. Numerical data were presented as Mean ± Slander deviation (SD), P* value<0.05 was considered statistically significant.

Regarding the heart rate and mean blood pressure there were neither clinical nor statistical differences among the four groups while the patients were under anesthesia and till the first-hour intra-operatively (Figures 2 and 3).

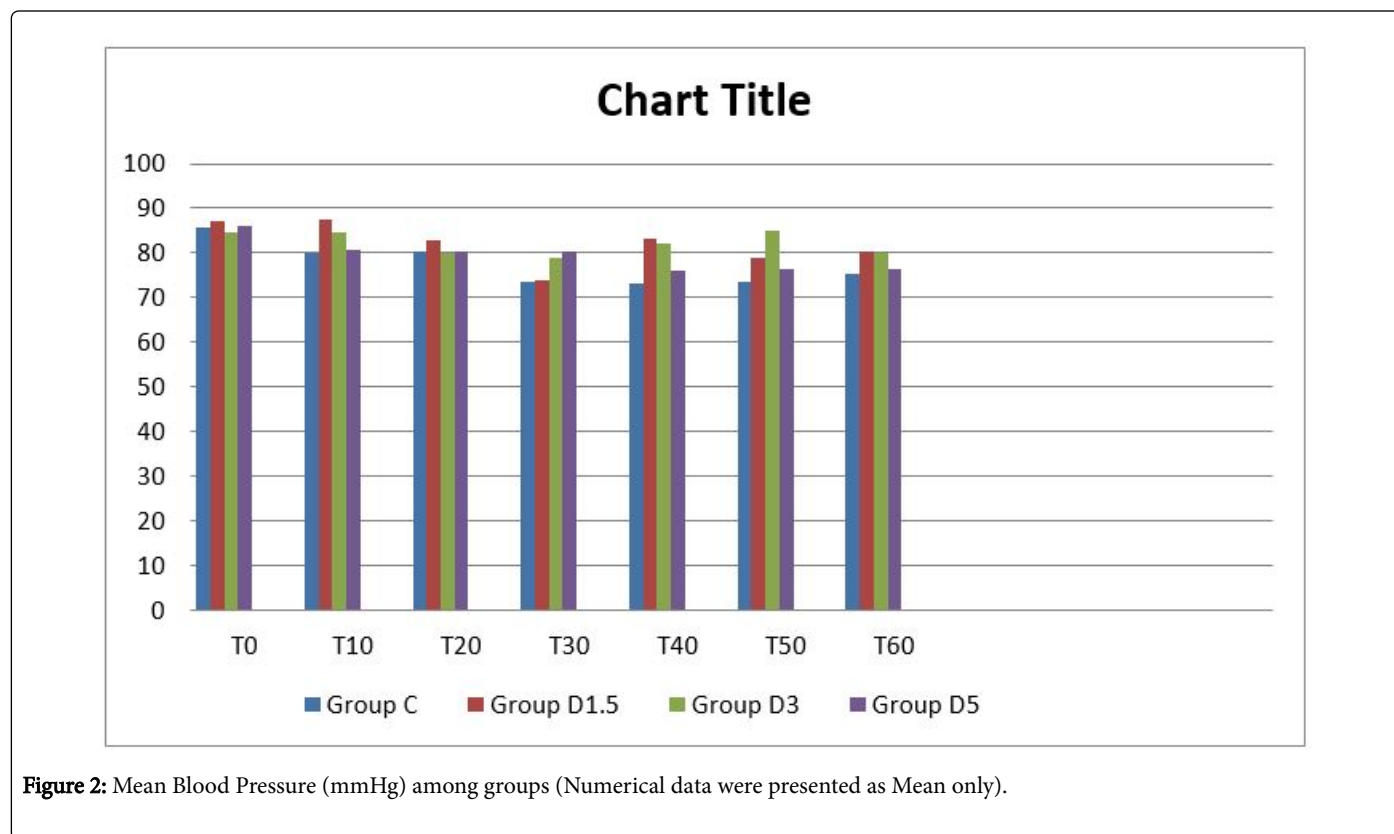


Figure 2: Mean Blood Pressure (mmHg) among groups (Numerical data were presented as Mean only).

Sedation score showed a statistical significance between the control group C on one hand and the other three groups D1.5, D3 and D5 on the other hand as Ramsay score was reached 2 after 30 min and kept on the same level for the next 180 min in all the study groups but maintained at 1 in the control group C (Table 3).

There were no complications recorded in all groups apart from few cases of nausea and vomiting with neither statistical nor clinical relevance (Table 4).

T30 min	1 (1-1)	2 (1-2) *	2 (1-2) *	2 (1-2) *	0.001
T60 min	1 (1-1)	2 (2-2) *	2 (2-2) *	2 (2-2) *	<0.001
T120 min	1 (1-1)	2 (2-2) *	2 (2-2) *	2 (2-2) *	<0.001
T180 min	1 (1-1)	2 (2-2) *	2 (2-2) *	2 (2-2) *	<0.001

*Denotes statistical significance compared to control group

Table 3: Ramsay sedation score values in different groups Values are presented as median (inter-quartile range).

	Group C (n=22)	Group D1.5 (n=21)	Group D3 (n=25)	Group D5 (n=26)	P value
T0	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1

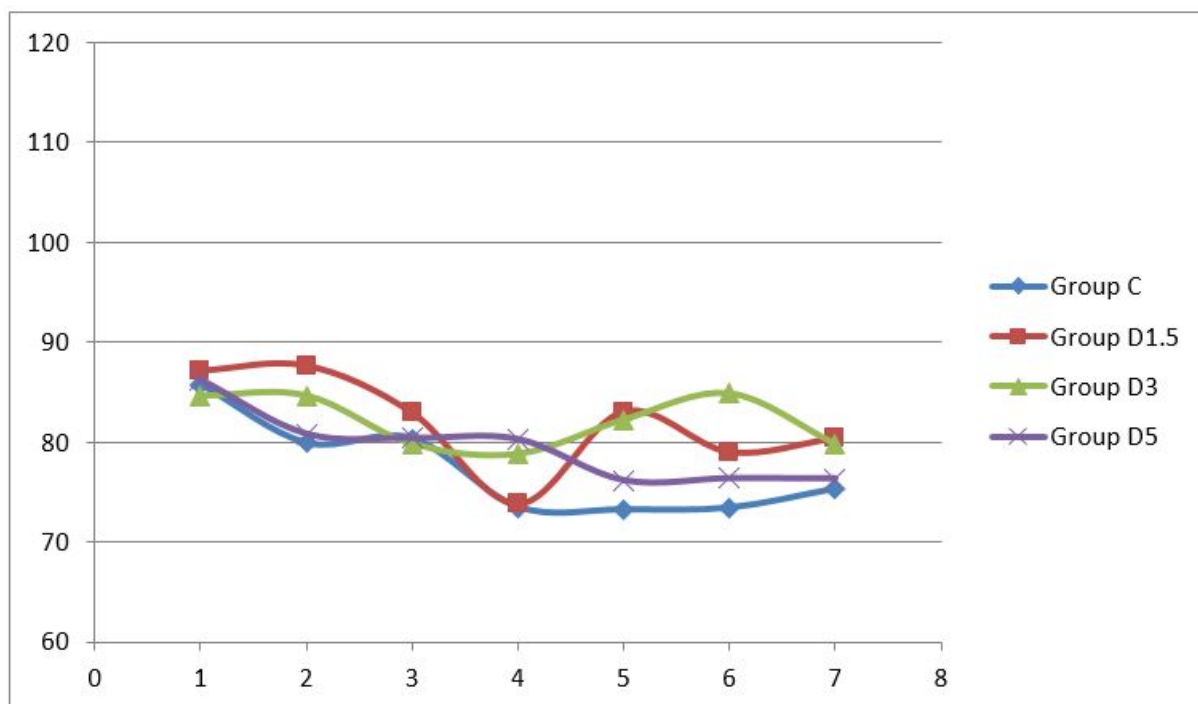


Figure 3: Heart rate changes in both groups.

	Group C	Group D1.5	Group D3	Group D5	P value
Nausea	1 (4.54%)	1 (4.76%)	2 (8%)	1 (3.84%)	1
Vomiting	0 (%)	1 (4.76%)	1 (4%)	0 (%)	1

Table 4: cases with complications (number of cases and percentage).

Discussion

This study is answering the question of; what is the least dose of Dexmedetomidine that will cause a clinical effect when injected intrathecally? It showed that there is an effect on the duration of the spinal anesthesia when Dexmedetomidine was added. There is a prolonged duration regarding both sensory and motor block. Moreover, there is a sedative effect which is favored in the spinal anesthesia. This sedative effect is safe and accepted and will encourage the usage of Dexmedetomidine in combination with levobupivacaine in spinal anesthesia. Likewise, there were a few adverse effects in the form of nausea and vomiting with neither statistical nor clinical relevance.

Also, this study showed that there is a relation between the dose of Dexmedetomidine and its effect. However, this relation has no statistical significance in small doses (1.5 µg) but has both clinical and statistical significance when increased to 3 µg and 5 µg respectively.

Although there was a sedative effect, this effect was very mild as it was scored as 2 in Ramsay score. These results conclude that there is a weak relation between Dexmedetomidine and the level of sedation if it was injected intrathecally.

We have chosen these doses under the theory that 1/10 dose of the drug will be effective when injected into the intrathecal space. This was tested before by Kanzani [2] in the humans but in a dose of 3 µg, he found that this dose is equivalent to 30 µg intravenously.

There were many studies that have tested the effect of Dexmedetomidine when injected into the cerebrospinal fluid either in animals or humans or with different doses in comparison with saline or Clonidine [2,9,10,14-22], however, this is the first study to test the same drug with different doses, especially with the very small dose 1.5 µg.

In this study, no cases were reported with hypotension or bradycardia to the limit of intervention. However, there is a study [23] reported more hypotension and sedation with the 5 mcg dose. The explanation of this difference may be because of the type of surgery (hysterectomy) mandated a higher level of block and consequently hypotension was reported.

This study has limitations in the form of the type of surgery as we did not restrict to a single type of surgery which may have an influence on the results. Moreover, adding Dexmedetomidine will not increase the sensory block duration alone, but also, will increase the duration of the motor block duration which considered as a limitation to the drug itself (not to the study) and may lead to prolonged recovery or hospital stay. Moreover, there is still a question regarding a dose of 2 µg which was not tested in this study and needs further research. In this study, the protocol was to start with 1.5 µg and increase in a manner of duplication and subsequently dose of 2 µg was not tested.

We concluded that Dexmedetomidine can prolong the duration of the spinal anesthesia with a high safety profile and no complications in both doses 3 and 5 µg but not with a dose of 1.5 µg.

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