Effect of dexmedetomidine added to spinal bupivacaine for urological procedures

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ABSTRACT

الأهداف: تحديد أثار أضافه ديكسمتيدوميدين إلى بوبيفاكاين في عمليات تخدير المحور العصبي.

الطريقة: أُجريت هذه الدراسة على 66 مريضاً في الجامعة الأردنية – عمان – الأردن، خلال الفترة مابين ابريل 2008م وحتى مايو 2008م. تم توزيع المرضى عشوائياً إلى ثلاثة مجموعات، تم إعطاء كل مجموعة جرعات مختلفة وذلك من (بوبيفاكاين) 12.5mg عن طريق السبيل الشوكي: (المجموعة–N) مع محلول الملحي، (المجموعة–D_5) ديكسمتيدوميدين 5µg، (المجموعة–D_{10}) ديكسمتيدوميدين 10µg. وتم تسجيل الزمن اللازم للوصول إلى إحصار الإحساس في مستوى ألفقره الصدرية العاشرة (T10) و الزمن اللازم للاحصار الحركي 3 حسب مقياس Bromage 3 ، وتم حساب الزمن الاضمحلالي لمستوى ألفقره العجزية الأولى (S1) وذلك للوصول لمقياس Bromage 0.

النتائج: الزمن الوسطي للوصول لمستوى احصار الإحساس في الفقرة الصدرية العاشرة (T10) كان (4.7±2.0) دقيقة، (6.3±2.7) دقيقة، (9.5±3.0) دقيقة، للمجوعات D_5، D_{10} وN على التوالي، أما الزمن للوصول للإحصار الحركي–3 حسب مقياس Bromage 3 كان (10.4±3.4) دقيقة، (13.0±3.4) دقيقة، (18.0±3.3) دقيقة للمجموعات D_5، D_{10}وN على التوالي، أما الزمن الاضمحلالي للقطاع العصبي الجلدي للفقرة العجزية الأولى (S1) كان (338.9±44.8) دقيقة، (277.1±23.2) دقيقة، و(165.5±32.9) دقيقة للمجموعات D_5، D_{10}و N على التوالي .والزمن الاضمحلالي للوصول لـ Bromage 0 كان (302.9±36.7) دقيقة، (246.4±25.7) دقيقة، (140.1±32.3) دقيقة للمجموعات D_5، D_{10} وN على التوالي، إن الزمن اللازم للاحصار العصبي، الحسي، الحركي والزمن الاضمحلالي كان واضحاً بمقارنة المجموعات مع بعضها: (N مع N – D_5 مع D_5 – D_{10} مع D_{10})، وكانت ($p<0.001$).

خاتمة: أن تأثير ديكسمتيدوميدين يعتمد على مقدار الجرعة المضافة إلى بوبيفاكاين وذلك في التخدير النصفي وهذا التأثير الحسي الحركي يعتمد على الجرعة المضافة.

Objectives: To determine the effect of adding dexmedetomidine to bupivacaine for neuraxial anesthesia.

Methods: Sixty-six patients were studied between April and May 2008 in the University of Jordan, Amman Jordan. They were randomly assigned into 3 groups, each receiving spinal bupivacaine 12.5mg combined with normal saline (group N) Dexmedetomidine 5µg (group D5), or dexmedetomidine 10µg (group D10). The onset times to reach T10 sensory and Bromage 3 motor block, and the regression times to reach S1 sensory level and Bromage 0 motor scale, were recorded.

Results: The mean time of sensory block to reach the T10 dermatome was 4.7±2.0 minutes in D10 group, 6.3±2.7 minutes in D5, and 9.5±3.0 minutes in group N. The mean time to reach Bromage 3 scale was 10.4±3.4 minutes in group D10, 13.0±3.4 minutes in D5, and 18.0±3.3 minutes in group N. The regression time to reach S1 dermatome was 338.9±44.8 minutes in group D10, 277.1±23.2 minutes in D5, and 165.5±32.9 minutes in group N. The regression to Bromage 0 was 302.9±36.7 minutes in D10, 246.4±25.7 minutes in D5, and 140.1±32.3 minutes in group N. Onset and regression of sensory and motor block were highly significant (N vesus D5, N versus D10, and D5 versus D10, $p<0.001$).

Conclusion: Dexmedetomidine has a dose dependant effect on the onset and regression of sensory and motor block when used as an adjuvant to bupivacaine in spinal anesthesia.

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Dexmedetomidine is an α2-adrenergic agonist that has been used for pre-medication, and as an adjunct to general anesthesia as well as a sole anesthetic agent and also as a sedation agent in the intensive care unit.[1-5] Dexmedetomidine has been used intrathecally in animals and was found to be a very potent antinociceptive agent when given intrathecally to rats.[6-8] It has been used in the epidural space in humans without any reports of neurological deficits.[9] Dexmedetomidine used intravenously as adjuvant agent to support spinal Prilocaine and significantly prolonged the sensory and motor block.[10] Small doses of dexmedetomidine (3 μg) used in combination with bupivacaine, in humans, for spinal anesthesia, has been shown to produce a shorter onset of motor block and a prolongation in the duration of motor and sensory block with preserved hemodynamic stability and lack of sedation.[11] Clonidine is an α2-adrenergic agonist that is often administered intrathecally in humans. It has been given in doses up to 450 μg in dosing studies, but it is not used often in this dose.[12-16] In animals, it was found that the duration of both sensory and motor block reached a plateau at 150 μg of clonidine.[17] On the basis of previous studies,[6,8] that showed a 1:10 dose ratio between intrathecal dexmedetomidine and clonidine, produced a similar effect in animal models, and the potency of an epidurally administered α2-adrenergic agonist was well correlated with their binding affinity to the spinal α2-adrenergic receptor, we used larger doses of Dexmedetomidine in the spinal anesthesia combined with bubivacaine than previous study to investigate the effect of adding this doses (5 μg and 10 μg) on the onset and regression of sensory and motor block together with hemodynamic and sedation changes versus intrathecal bupivacaine alone. The purpose of this study was to determine the effect of adding different doses of dexmedetomidine to bupivacaine for neuraxial anesthesia.

Methods. After obtaining the Ethical Committee approval from the Faculty of Medicine in the University of Jordan, and written informed consent, 66 patients ASA (American Society of Anesthesiologists) grade I-III scheduled for transurethral resection of prostate (TURP), transurethral resection of bladder tumors (TURBT) or placement of tension-free vaginal tape (TVT) for urinary incontinence control, were enrolled in the study from April 2008 to May 2008. The study took place in University of Jordan. Patients using α2-adrenergic receptors antagonists, calcium channel blockers, angiotensin converting enzyme inhibitors, or noted to have dysrhythmias on the electrocardiogram (ECG), a body weight of more than 120 kg, or height less than 150 cm were excluded from the study. Standard monitoring was used, including non-invasive arterial blood pressure (BP), ECG, heart rate (HR) and pulse oximetry (SpO_2). All the patients received 4 L/minutes of O_2 by face mask. With the patient in the sitting position, spinal anesthesia was performed at the level of L3-L4 through a midline approach using a 25-gauge Quincke spinal needle (B/Braun Medical, Melsungen, Germany) with the bevel pointing upwards. Using a computer-generated random numbers inserted into sealed envelops marked 1-66, the patients were divided into 3 groups of 22 patients. The dose of isobaric 0.5% bupivacaine, 12.5 mg (2.5 ml), was identical in all study groups. Patients allocated to group D5 received isobaric 0.5% bupivacaine, 12.5 mg + 5 μg dexmedetomidine diluted with preservative free normal saline with a concentration of 10 μg/1 ml (Precedex 100 μg/ml; Hospira, Inc). Patients allocated to group D10 received isobaric 0.5 % bupivacaine, 12.5 mg + 10 μg dexmedetomidine diluted with preservative free normal saline with a concentration of 20 μg/1 ml. Patients allocated to group N received isobaric 0.5% bupivacaine, 12.5 mg + 0.5 ml preservative free normal saline. All the patients received a volume of 3 ml intrathecal drug. The intrathecal drug formula was prepared by a separate anesthesiologist and under a sterile technique given to the physician who performed the spinal anesthesia and who was blind to the group to which the patient was allocated and the solution being injected. The anesthesiologist performing the block recorded the baseline value of vital signs (BP, HR, SpO_2,) and after performing the spinal anesthetic, the vital signs were recorded at 2, 5, and every 5 minutes in the operating room and every 15 minutes in the Post Anesthesia Care Unit (PACU) until the patient was discharged to his ward. The sensory dermatome level was assessed by cold sensation using an alcohol swab along the mid-clavicular line bilaterally. The motor dermatome level was assessed according to the modified Bromage scale: 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 is able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle.[18] The sensory level and Bromage scale were recorded pre-spinal injection, and every 2 minutes after the spinal injection up to the 10th minute and after that every 3 minutes until the highest dermatome was reached. In the PACU, the sensory level and Bromage scale were recorded every 15 minutes until the patient was discharged from the PACU. The times to reach the T10 dermatome and to reach Bromage 3 before surgery were recorded, and the times to regression to the S1 dermatome and to reach Bromage 3 in PACU were recorded. All durations were calculated considering the time of spinal injection as time

zero. When sensory levels of anesthesia were not equal bilaterally, the higher level was used for the statistical analysis. Patients were discharged from the PACU after sensory regression to the S1 segment, and Bromage scale of 0. For the purpose of the study, hypotension was defined as a systolic blood pressure of <90 mm Hg and Bradycardia was defined as HR <50 beats/minute. The patients did not received any premedication in either the surgical floor or the operation room. The level of sedation was evaluated intraoperatively and post-operatively every 15 minutes using the Ramsay sedation scales: scale 1 - patient anxious, agitated, or restless; scale 2 - patient cooperative, oriented, and tranquil alert; 3, Patient responds to commands; 4, Asleep, but with brisk response to light glabellar tap or loud auditory stimulus; scale 5 - asleep, sluggish response to light glabellar tap or loud auditory stimulus and sclae 6 - asleep, no response.[19]

All patients were contacted in floor after 24 hours by the anesthesiologist doctor and in the outpatient clinic 2 weeks following discharge by the surgeon doctor. The doctors assessed for any new onset of neurological impairment related to spinal anesthesia such as back, buttock or leg pain, headache or any new neurological deficit or complication.

Statistical analysis was performed using Statgraphics Centurion XV (Statpoint, Herdon, Virginia, USA). Data were expressed as either mean and standard deviation or numbers and percentages. The demographic data of patients were studied for each of the 3 groups. Continuous covariates (age, body mass index, and duration of surgery) were compared using analysis of variance (ANOVA). For categorical covariates (gender, ASA class, blood transfusion, nausea/vomiting, hypotension, bradycardia, use of ephedrine, use of additive analgesia, the use of atropine and type of surgery) a Chi-square test was used, with the p value reported at the 95% confidence interval. For the times to reach T10 dermatome, Bromage 3 scale, and the regression of the sensory block to S1 dermatome and Bromage scale 0, ANOVA test was used to compare the means. The level of significance used was $p<0.05$. The total sample size was calculated to be 42 (14 patients in each group). Power analysis using the following parameters was carried out (α =0.05, β =0.80, sensory regression time = 30 minutes, standard deviation = 28 minutes). We increased the total number of patients to increase the power of our study.

Results. Sixty-six patients were enrolled in the study. One patient from group D5 and another one from group D10 were excluded from further analyses; because of the conversion of surgery to an open technique in both patients. Sixty-four patients completed the study protocol and were included in the data analysis. Thus, group N consisted of 22, group D5 of 21, and group D10 of 21 patients. Demographic data did not differ between the 3 study groups (**Table 1**).

The time to reach T10 dermatome, Bromage 3 scale, the regression of the sensory block to S1 dermatome, and Bromage scale 0 were affected by the addition of Dexmedetomidine to the spinal bupivacaine in a dose dependent manner. The block onset and regression times in minutes are shown in **Table 2**.

The total amount of fluids administered following spinal anesthesia, the duration of surgery, need to give ephedrine or atropine, bradycardia, hypotension, need of additive analgesia, blood transfusion and nausea or

Table 1 - Demographic data.

Demographic data	Group N (n=22)	Group D5 (n=21)	Group D10 (n=21)	*P* value
Age (years)	63.9 ± 10.1	63.2 ± 10.2	66.1 ± 10.3	0.65
Gender				0.99
Male	17	16	16	
Female	5	5	5	
Body mass index	28.5 ± 4.7	28.4 ± 4.4	27.4 ± 3.9	0.68
ASA				0.772
I	3	3	5	
II	17	17	12	
III	2	1	5	
Surgery				0.462
TURT	8	9	8	
TURP	9	7	8	
TVT	5	5	5	

Values are expressed as mean±SD or numbers.
ASA - American Society of Anesthesiologists, TURT - trans urethral resection of tumor, TURP - trans urethral resection of prostate, TVT - tension-free vaginal tape

Table 2 - Block onset and regression times in minutes.

Characteristics of spinal block	Group N (n=22)	Group D5 (n=21)	Group D10 (n=21)	*P*-value
Sensory block to reach T10 dermatome	9.5 ± 3.0	6.3 ± 2.7	4.7 ± 2.0	<0.001
Motor block to reach Bromage 3	18.0 ± 3.3	13.0 ± 3.4	10.4 ± 3.4	<0.001
Sensory regression to S1 segment	165.5 ± 32.9	277.1 ± 23.2	338.9 ± 44.8	<0.001
Motor block regression to Bromage 0	140.1 ± 32.3	246.4 ± 25.7	302.9 ± 36.7	<0.001
Values are expressed as mean±SD.				

Table 3 - Surgical characteristics, adverse events and treatment.

Surgical characteristics	Group N (n=22)	Group D5 (n=21)	Group D10 (n=21)	*P*-value
Total intravenously infusion (ml)	909.6 ± 293.6	881.1 ± 209.7	1015.0 ± 294.3	0.28
Duration of surgery (min)	42.9 ± 7.9	45.9 ± 14.3	49.2 ± 24.3	0.48
Blood transfusion	1	2	2	0.79
Additive analgesia	1	1	0	0.62
Nausea/vomiting	1	0	1	0.62
Bradycardia	2	1	0	0.38
Hypotension	4	0	1	0.07
Atropine	0	0	0	not significant
Ephedrine	3	0	1	0.18
Values are expressed as mea±SD or numbers.				

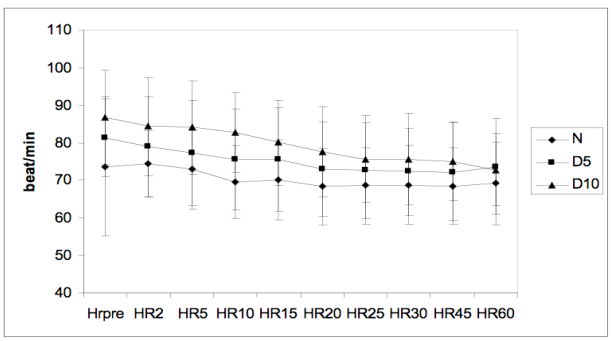

Figure 1 - Heart rate (HR) in the operating room. Values are the mean±SD. No significant differences were noted between the 3 groups.

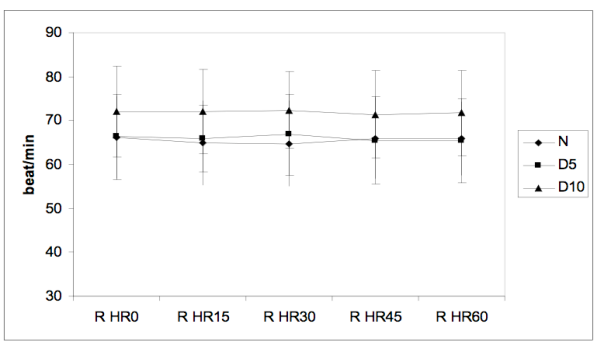

Figure 3 - Heart rate (HR) in the recovery room. Values are the mean±SD. No significant differences were noted between the 3 groups.

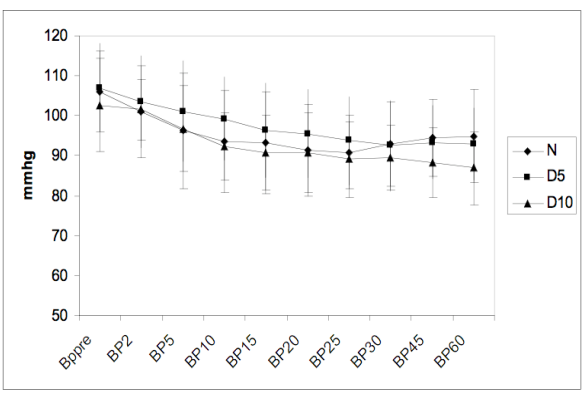

Figure 2 - Mean arterial pressure (MAP) in the operating room. Values are the mean±SD. No significant differences were noted between the 3 groups.

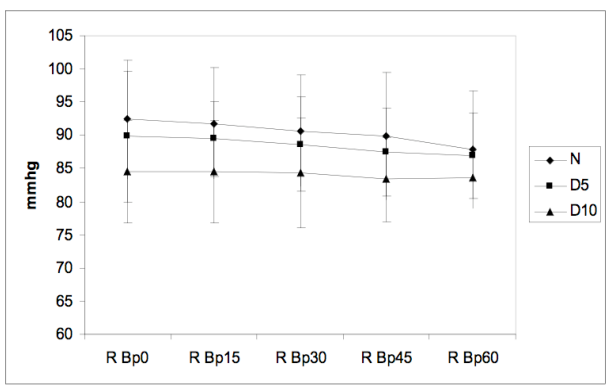

Figure 4 - Mean arterial pressure (MAP) in the recovery room. Values are the mean±SD. No significant differences were noted between the 3 groups.

vomiting in the intraoperative or PACU time were comparable in the three groups; $p>0.05$ (**Table 3**). Ramsay sedation scores were 2 in all patients in the 3 groups in the intraoperative and the PACU time. The mean values of mean arterial pressure and the heart rate in the first hour after performing the spinal anesthesia and the first hour in the PACU were comparable between the 3 groups (**Figures 1-4**). The SpO_2 was higher than 95% in all patients in the 3 groups either in the intraoperative or in the PACU time. Twenty-four hours and 2 weeks following discharge follow up did not show any neurological impairment related to spinal anesthesia such as back, buttock or leg pain, headache or any new neurological deficit.

Discussion. Different agents, such as epinephrine, phenylephrine, adenosine, magnesium sulfate, and clonidine, have been used as adjuncts for prolonging the duration of spinal anesthesia. Dexmedetomidine was used in a small dose (3 μg) in the spinal block combined with bupivacaine without any significant hemodynamic instability or sedation.[11] A larger dose of dexmedetomidine (1.5-2 μg/kg) was used in the epidural space for postoperative pain relief or to decrease the incidence of postoperative shivering in humans without any reports of neurological deficit.[9,20] The largest dose of recorded intrathecal dexmedetomidine, 100 μg, was used in a sheep model, where a 7-day follow-up showed no neurological deficits in the studied animals.[21] In our patients, we used dexmedetomidine in doses of 5 μg and 10 μg and the 2-week follow up showed no neurological deficit or any complaint from the patients regarding the spinal anesthesia. A dose of 1:10 ratio between intrathecal dexmedetomidine and clonidine produced a similar effect in animal models.[6,8] This theory was supported when dexmedetomidine was used for the first time in spinal anesthesia in humans, and Kanazi et al[11] showed that dexmedetomidine (3 μg) and clonidine 30 mg have an equipotent effect. Asano et al[7] showed that the potency of epidurally administered α2-adrenergic agonists was well correlated with their binding affinity to spinal α2-adrenergic receptors. Strebel et al[22] concluded in their study, that small doses of intrathecal clonidine (≤150 μg) significantly prolonged the anesthetic and analgesic effects of bupivacaine in a dose-dependent manner and that 150 μg of clonidine seems to be the preferred dose, in terms of effect versus unwarranted side effects, when prolongation of neuraxial anesthesia is desired. The binding affinity of dexmedetomidine compared with clonidine is approximately 1:10. Thus, we hypothesized that 5 μg and 10 μg of intrathecal dexmedetomidine might be equipotent to 50 μg and 100 μg of intrathecal clonidine respectively. Most of the previous clinical studies involved in the use of intrathecal α2-adrenergic agonists have been described with clonidine. The use of intrathecal clonidine has a well-established synergistic effect with local anesthetics.[22-24] The mechanisms by which intrathecal α2-adrenergic agonists prolong the motor and sensory block of local anesthetics is not clear. It may be an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetic and the α2-adrenergic agonist. The local anesthetic acts by blocking sodium channels, whereas the α2-adrenergic agonist acts by binding to pre-synaptic C-fibers and post-synaptic dorsal horn neurons. Intrathecal α2-adrenergic agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons.[25] This antinociceptive effect may explain the prolongation of the sensory block when added to spinal anesthetics. Intrathecal α2-adrenergic agonists can cause a dose-dependent decrease in motor strength in animals.[26] The prolongation of the motor block of spinal anesthetics may result from the binding of α2-adrenergic agonists to motor neurons in the dorsal horn.[27] In our study also, the dose of 5 μg and 10 μg of intrathecal dexmedetomidine added to 12.5 mg of bupivacaine compared with bupivacaine alone did not cause a significant decrease in blood pressure or the heart rate intraoperatively or in the PACU (**Figures 1-4**). Patients with a small dose of spinal dexmedetomidine (3 μg), having even received 5 mg of diazepam orally as pre-medication, had low sedation scores.[11] In our study, we used 5 μg and 10 μg of spinal dexmedetomidine without pre-medicating our patients with any type of benzodiazepines, and it did not affect the level of consciousness, and all our patients in the 3 groups had a Ramsay sedation score of 2. This result, with this dose of dexmedetomidine, does not contradict the other results when using an equipotent dose of clonidine. Kanazi et al[11] found in their study, that the supplementation of bupivacaine (12 mg) spinal block with a low dose of dexmedetomidine (3 μg) produces a significantly shorter onset of motor block, and a significantly longer sensory and motor block than bupivacaine alone. Our results, with the usage of a higher dose (5 μg and 10 μg) of dexmedetomidine, support the previous conclusion and add to it that this effect is dose dependent. In addition, we found that the onset of sensory block to reach T10 dermatome was shorter with the usage of dexmedetomidine in a dose dependant manner. The possible explanation of why we have a significant onset of sensory block in our results is that: we used a higher dose of dexmedetomidine than Kanazi et al[11] and we used a larger volume injected into the subarachnoid space. The assessment of onset of loss of sensation in our patients was every 2 minutes from the spinal injection for 10 minutes and continued every 3 minutes and this

is more frequent than Kanazi et al[11] patients' assessment, which started after 6 minutes and continued every 3 minutes.

A potential limitation of our study design was setting the upper limit of the tested dose range at 10 μg of dexmedetomidine. Therefore, we do not know if this dose dependence continues or where the optimal dose may lie.

In conclusion, our study of dexmedetomidine precipitated the onset of sensory and motor block, and it prolonged the sensory and motor block significantly when used with bupivacaine in spinal anesthesia in a dose dependent manner. Because of the absence of significant adverse effects, we endorse the addition of dexmedetomidine to spinal anesthesia bupivacaine when prolongation of spinal anesthesia is desired, for example, anesthesia for total hip or total knee surgery. Increasing the dexmedetomidine dose with spinal bupivacaine more than 10 μg needs further study.

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