INTRAVENOUS DEXMEDETOMIDINE PROLONGS BUPIVACAINE SPINAL ANALGESIA

MAHMOUD M AL-MUSTafa*, IZDIAD Z BADRAN**, HAMDI M ABU-ALI***, BASSAM A AL-BARAZANGI*, ISALM M MASSAD* AND SUBHI M. AL-GHANEM****

Abstract

Background: The prolongation of spinal anesthesia by using clonidine through the oral, intravenous and spinal route has been known. The new α₂ agonist, dexmedetomidine has been proved to prolong the spinal anesthesia through the intrathecal route. We hypothesized that dexmedetomidine when administered intravenously following spinal block, also prolongs spinal analgesia.

Methods: 48 patients were randomly allocated into two equal groups following receiving spinal isobaric bupivacaine 12.5 mg. Patients in group D received intravenously a loading dose of 1 μg/kg dexmedetomidine over 10 min and a maintenance dose of 0.5 μg/kg/hr. Patients in group C (the control group) received normal saline. The regression times to reach S1 sensory level and Bromage 0 motor scale, hemodynamic changes and the level of sedation were recorded.

Results: The duration of sensory block was longer in intravenous dexmedetomidine group compared with control group (261.5 ± 34.8 min versus 165.2 ± 31.5 min, P <0.05). The duration of motor block was longer in dexmedetomidine group than control group (199 ± 42.8 min versus 138.4 ± 31.3 min, P <0.05).

Conclusion: Intravenous dexmedetomidine administration prolonged the sensory and motor blocks of bupivacaine spinal analgesia with good sedation effect and hemodynamic stability.

Keywords: Anesthesia, spinal; dexmedetomidine; bupivacaine; intravenous.

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Introduction

Spinal analgesia is a well-known technique used in urological procedures; transurethral resection of prostate (TURP), transurethral resection of bladder tumors (TURT) or Tension-free Vaginal Tape (TVT). The operative blood loss in TURP and TURT in spinal anesthesia is less in comparison to inhalational general anesthesia. An intra-operative cough test helps to correctly position the tape in the TVT surgery during spinal anesthesia.

Different agents, like epinephrine, phenylephrine, adenosine, magnesium sulfate and clonidine, have been used as adjuncts to local anesthesia for prolonging the duration of spinal analgesia via the intrathecal route. Small doses of dexmedetomidine (3 μg) used in combination with bupivacaine in humans in spinal anesthesia produces 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. Clonidine an α₂-agonists, has been used widely in the intrathecal route. It has been used intravenously within one hour after the spinal block and found that it prolonged bupivacaine spinal anesthesia for approximately one hour without adverse effect.

Dexmedetomidine, also an α₂-agonist, has been used for pre-medication and as an adjunct to general anesthesia. Intravenous Dexmedetomidine decreases the inhalational anesthesia and opioid requirements during general anesthesia. We hypothesize that intravenous dexmedetomidine, might prolong the duration of spinal analgesia similar to clonidine.

The aim of this study, therefore was to evaluate the prolongation of spinal analgesia by the intravenous dexmedetomidine administration after the spinal block, and to assess the hemodynamic changes and the level of sedation.

Methods and Materials

Following approval of the Ethical Committee and obtaining written informed consent from patients, forty eight patients, ASA I-III, scheduled for TURP, TURT or TVT were enrolled in the study. Patients using α₂-adrenergic receptors antagonists, calcium channel blockers, angiotensin converting enzyme inhibitors, having dysrhythmia by ECG, body weight more than 120 Kg, or height less than 150 cm, were excluded from the study. All patients were pre-hydrated with 300 ml of Ringer’s Lactate solution via an 18-gauge IV cannula in the dorsum of the hand. Standard monitoring was used, including non-invasive arterial blood pressure (BP), ECG, heart rate (HR) and pulse oximetry. Patient motor power and sensation to cold using alcohol solution up to T10 dermatome were examined in both lower extremities. All patients received 4 L/min of O₂ by simple face mask.

With the patient in the sitting position, spinal analgesia was performed at the level of L3-L4 through a midline approach using a 25-gauge Quincke spinal needle (B/Braun Medical, Messenger, Germany) with the hole pointing upwards. If the spinal block failed at the level of L3-L4, we changed the level to L2-L3. In case of failure at both levels; the procedure was abandoned, general anesthesia administered and those patients were excluded from the study. The spinal injection rate of bupivacaine 0.5% was 1ml/3-4 seconds in all patients. Using a computer-generated random list, patients were divided into two groups of 24 each. Control group (group C), received normal saline intravenously and the dexmedetomidine group (group D), received intravenous dexmedetomidine.

Isobaric 0.5 % bupivacaine, 12.5 mg (2.5 ml), was injected intrathecally in all patients. 50 cc syringe was prepared with either normal saline or dexmedetomidine. (Precedex 100 µg/ml; Hospira, Inc.) diluted with normal saline in a concentration of 4μg/ml. Immediately after spinal analgesia patients were laid back to supine position. Patients allocated to group D received intravenously through the intravenous infusion pump a loading dose of 1 μg/kg/hr dexmedetomidine over 10 min and a maintenance dose of 0.5 μg/kg/hr till the end of surgery. Patients in group C received also in 10 min, the same calculated volume normal saline of loading and maintenance dose as in group D.

The intravenous formula was prepared by an anesthetist doctor and was passed on to the doctor who performed the spinal analgesia who was blinded as to which group the patient was allocated. The anesthesiologist to perform the block recorded the baseline value of vital signs (blood pressure, heart rate...
and peripheral oxygen saturation). After performing the spinal block, the vital signs were recorded at 2, 5, and every 5 minutes in the operation room and every 15 minutes in the Post Anesthesia Care Unit (PACU) until the patient was discharged to his ward, after having achieved complete reversal of sensory and motor block.

In the PACU, the sensory level and Bromage scale was recorded every 15 minutes until the patient was discharged from the PACU. The times of regression to the S1 dermatome and reach Bromage scale 3 in PACU were recorded. The sensory level was assessed by cold sensation using alcohol swab along the mid-clavicular line bilaterally. The motor 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. 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 0.

For the purpose of this study, hypotension was defined as a systolic blood pressure of less than 90 mmHg and if maintained, was treated with a bolus administration of 300 ml of lactated Ringer’s solution over 10 min and 6 mg of intravenous ephedrine. Bradycardia was defined as HR <50 beats/min, and if maintained was treated with 0.5 mg of intravenous atropine.

The level of sedation was evaluated intra-operatively and post-operatively every 15 min using Ramsey Level of Sedation Scale:
1. Patient anxious, agitated, or restless;
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;
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus.
6. Asleep, no response.

All sedation scores were recorded considering the time of start infusion as time zero.

Two weeks following discharge, all patients were evaluated in the outpatient clinic. The doctor in charge assessed any new onset of neurological impairment related to spinal anesthesia such as back, buttock or leg pain, headache or any new neurological deficit.

Statistical Methods

Statistical analysis was done using statgraphics Centurion XV (Statpoint, Herdon, Virginia – USA). Data was expressed as either mean and standard deviation or numbers and percentages. The demographic data of patients were studied for each of the three groups. The means of the continuous variables (Age, BMI, and duration of surgery) were compared between the three groups using analysis of variance ANOVA, while the demographic data for the categorical variables (sex, ASA class) were compared using chi-square test. Adverse effects and treatment factors (blood transfusion, nausea/vomiting, occurrence of hypotension, bradycardia, use of ephedrine, use of additive analgesia, the use of atropine) were also compared using the chi-square test. The P value of <0.05 was considered significant.

Results

Forty eight patients (Cn = 24) (Dn = 24) were enrolled, completed the study protocol and were included in the data analysis. The demographic data did not differ between the two study groups (Table 1).

<p>| Table 1 |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Demographic data. Values are the means ± standard deviations or numbers</th>
<th>C (n=24)</th>
<th>D (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.2 ± 9.7</td>
<td>64.7 ± 12.5</td>
<td>0.87</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>19/5</td>
<td>19/5</td>
<td>P=NS</td>
</tr>
<tr>
<td>BMI</td>
<td>28.1 ± 4.6</td>
<td>26.6 ± 3.7</td>
<td>0.23</td>
</tr>
<tr>
<td>ASA I/II/III</td>
<td>19/3/2</td>
<td>18/4/2</td>
<td>0.76</td>
</tr>
<tr>
<td>Surgery – TURT/ TURP/TVT</td>
<td>10/9/5</td>
<td>10/9/5</td>
<td>P = NS</td>
</tr>
</tbody>
</table>
Time to regression to S1 dermatome and Bromage scale 0, was significantly prolonged in group D in comparison with group C. The regression time to S1 in group C was 165.2 ± 31.5 min and group D 261.5 ± 34.8 min, the P value < 0.0001. The regression time to reach the Bromage 0 scale was 138.4 ± 31.3 min in group C and 199.9 ± 42.8 min in group D, the P value < 0.0001 (Table 2).

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>C (n=24)</th>
<th>D (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor block regression to Bromage 0</td>
<td>138.4 ± 31.3</td>
<td>199.9 ± 42.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sensory regression to S1 segment</td>
<td>165.2 ± 31.5</td>
<td>261.5 ± 34.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The duration of surgery, need to give ephedrine or atropine, bradycardia, hypotension, need to additive analgesia, blood transfusion, nausea or vomiting in the intraoperative or PACU time, were comparable in the two groups (P > 0.05). The total amount of fluids administered following spinal anesthesia was higher in group C as compared to D group (910.8 ± 280.1 versus. 864.5 ± 172.8; p = 0.025) (Table 3).

**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>C (n=24)</th>
<th>D (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IV infusion</td>
<td>910.8 ± 280.1</td>
<td>864.5 ± 172.8</td>
<td>0.025</td>
</tr>
<tr>
<td>Duration of Surgery</td>
<td>42.8 ± 7.5</td>
<td>45.1 ± 8.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>1/23</td>
<td>1/23</td>
<td>0.46</td>
</tr>
<tr>
<td>Additive analgesia</td>
<td>1/23</td>
<td>0/24</td>
<td>0.58</td>
</tr>
<tr>
<td>Nausea&amp;Vomiting</td>
<td>1/23</td>
<td>0/24</td>
<td>0.32</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2/22</td>
<td>4/20</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4/20</td>
<td>0/24</td>
<td>0.15</td>
</tr>
<tr>
<td>Atropine</td>
<td>0/24</td>
<td>2/22</td>
<td>0.65</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>1/23</td>
<td>0/24</td>
<td>0.60</td>
</tr>
</tbody>
</table>

The mean values of mean arterial pressure in the first hour after performing the spinal anesthesia and the first hour in the PACU (Recovery room) were comparable between the tow groups (Fig. 1).

The mean value of heart rate was significantly decreased in group D in comparison to group C in the first hour in the operation room and comparable in the PACU (Fig. 2).

Ramsey sedation scale was 2 in all patients in group C, and ranged from 2-5 in group D, the maximum score was 5 in 3 patients, 4 in 19 patients, and 3 in one patients, and the maximum mean score of sedation (3.96 ± 0.55) was achieved 30 min after starting dexmedetomidine infusion (Fig. 3).

The oxygen saturation was higher than 95% in all patient in the two groups either in the intraoperative or in the PACU time.

Two weeks following discharge from the outpatient clinic, the follow up did not show any neurological impairment related to spinal analgesia such as back, buttock or leg pain, headache or any new neurological deficit.

**Discussion**

Different drugs have been used as adjuvant to local anesthesia in order to prolong the duration of spinal analgesia. Clonidine an α₂ agonist, has been used widely in the intrathecal, oral and intravenous routes to prolong the duration of spinal analgesia. It is known to have prolonging effect on sensory and motor blocks when used as an oral premedication within 2 h before bupivacaine spinal anesthesia. The intravenous administration of clonidine within 1 h after the spinal block prolonged bupivacaine spinal analgesia for approximately 1 h without adverse effect.

Dexmedetomidine, also an α₂ agonist, is pharmacologically related to clonidine, has 8 times more affinity for α₂ receptors than does clonidine. It produces sedation and anxiolysis by binding to α₂ receptors in the locus ceruleus, which diminishes the release of norepinephrine and inhibits sympathetic activity, thus decreasing heart rate and blood pressure. It produce analgesia by binding to adrenoreceptors in the spinal cord. It has been used as adjuvant to local anesthesia in the intrathecal route and has significant effect on onset and duration of spinal anesthesia.

Dexmedetomidine has an onset of action of 30 min when the maintenance dose is used intravenously. Use of standard loading dose is used (1 µg/Kg/hr infused over 10 minutes) decreases the onset of action of dexmedetomidine. Side effects of dexmedetomidine,
**Fig. 1**
Comparison of Mean arterial pressure (MAP) levels among group C and D in first hour after spinal analgesia and first hour in Recovery room (R). Values are expressed as mean ± SD

![Graph of Mean arterial pressure (MAP) levels among group C and D.](image1)

**Fig. 2**
Comparison of Heart Rate (HR) levels among group C and D in first hour after spinal analgesia and first hour in Recovery room (R). Values are expressed as mean ± SD

![Graph of Heart Rate (HR) levels among group C and D.](image2)

**Fig. 3**
Comparison of Ramsay sedation score among group C and D. Values are expressed as mean ± SD

![Graph of Ramsay sedation score among group C and D.](image3)
such as hypotension and bradycardia, are dose dependent. Infusion of loading dose over 10 min and then infusing the maintenance dose decreases the incidence of those side effects.

Jorm et al\textsuperscript{13} found that dexmedetomidine has an inhibitory effect on the locus ceruleus (A6 group) located at the brain stem. This supraspinal action could explain the prolongation of spinal anesthesia after intravenous administration of dexmedetomidine. The noradrenergic innervation of the spinal cord arises from the noradrenergic nuclei in the brain stem including the locus ceruleus, the A5, and the A7 noradrenergic nuclei. Neurons in the locus ceruleus are connected to the noradrenergic nuclei in the brain stem. Axon terminals of the noradrenergic nuclei reach lamina VII and VIII of the ventral horns of the spinal cord. The activity of the noradrenergic neurons is decreased by agonists acting at α\textsubscript{2}-adrenergic receptors on the locus ceruleus cell bodies. Therefore, inhibition of the locus ceruleus results in disinhibition of the noradrenergic nuclei and exerted descending inhibitory effect on nociception in the spinal cord\textsuperscript{15}. In group D, the prolongation of motor block is less in comparison to its sensory block (199.9 ± 42.8 min versus 261.5 ± 34.8 min). The mechanism of motor block is unclear, the analgesic effects of α\textsubscript{2}-adrenergic agonists could be mediated through supraspinal, spinal, and peripheral actions\textsuperscript{16}. There is some evidence that clonidine results in direct inhibition of impulse conduction in the large, myelinated A\textalpha fibers and the 50\% effective concentration (EC\textsubscript{50}\%) measured approximately 4-folds of that in small, unmyelinated C fibers\textsuperscript{17}. This could explain the less prolonged motor block compared with sensory block, as conduction of motor nerve fibers was less inhibited than sensory nerve fibers at the same concentration of clonidine. The same process might be applied to dexmedetomidine, and would explain the more sensory than motor block prolongation.

Dexmedetomidine is known to have sedation effect\textsuperscript{18}; providing better conditions for the surgeon and the patient, provided that hemodynamic stability is preserved. In our patients, Ramsay sedation scores ranged from 2-5, the maximum score in group D was 3.96 ± 0.55. The heart rate decreased significantly after the start of intravenous infusion loading dose and extended in the PACU (Fig. 2). This decrease in the heart rate was more clear and significant in group D in comparison with group C. The lower HR observed in group D could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by dexmedetomidine\textsuperscript{19,20}. Other studies support the finding that the bradycardia effect of dexmedetomidine is long lasting when used as a premedication drug\textsuperscript{21,22}. Six patients developed bradycardia (HR <50 beat/min), only two patients in group D needed to have atropine to reverse the bradycardia, and statistically and clinically this was not significant.

Previous studies have shown that the hypotensive effect of dexmedetomidine persists in the intraoperative as well as in the postoperative period\textsuperscript{22,23}. In our patients the mean arterial pressure was also decreased in the D group as well as the C group (Fig. 1) and clinically was not significant. There was no further decrease in the blood pressure after adding intravenous dexmedetomidine to spinal anesthesia. Only one patient in group C received ephedrine because of decrease the systolic blood pressure lower than 90 mmHg, which statistically was not significant. The total intravenous fluid administered during surgery was less in group D in comparison with group C (864.5 ± 172.8 versus 910.8 ± 280.1, p = 0.025).

In conclusion, supplementation of spinal anesthesia with intravenous dexmedetomidine produces significantly longer sensory and motor block than spinal analgesia alone. Adverse side effects were avoided by the slow infusion of loading and the maintenance dose of dexmedetomidine. All patients reached good sedation levels that enabled their cooperation and better operating conditions for the surgeon without significant respiratory depression.
References


