Comparison of Two Different Doses of Dexmedetomidine as an Adjuvant to Intrathecal Bupivacaine in Patients Undergoing Femur Surgery.

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ABSTRACT

Background: Duration of action of local anaesthetic is an important limiting factor in spinal anaesthesia. Dexmedetomidine, selective α-2-agonist has been recently used in addition to other adjuvants to prolong the duration of intrathecal local anaesthetics. Aim: To compare two different doses of dexmedetomidine added to heavy bupivacaine 0.5% intrathecally for femur surgeries. Methods: In this prospective double blind trial, one hundred and twenty patients were randomly allocated into two groups, D1 and D2. Group D1 received 12.5 mg 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine. Group D2 received 12.5 mg 0.5% hyperbaric bupivacaine and 10 μg dexmedetomidine. Results: Sensory and motor block were comparable in both groups in terms of characteristics like the highest level of sensory block achieved, time to achieve maximum sensory block and duration of regression to Bromage scale 0. However time of first analgesic request and total analgesic requirement were significantly reduced by increasing intrathecal dose of dexmedetomidine to 10 μg without any undesirable effects. Conclusion: Intrathecal dose of 10 μg dexmedetomidine provided an increased duration of sensory compared to 5 μg dosing, with no significant increase in duration of motor blockade or the incidence of hypotension, bradycardia and any other undesirable side-effects.

Keywords: Analgesic, α-2 agonist, Intrathecal Dose, Motor Blockade, Spinal Anaesthesia.

INTRODUCTION

Orthopaedic fixations in lower extremity has conventionally and preferable been performed under spinal anaesthesia. Though, cost effective and easy to perform, the major limitation observed frequently is the limited duration of action, which requires conversion of anaesthetic technique or early analgesic intervention in post-operative period.¹ The list of various intrathecal adjuvants that have been used for prolongation and intensifying the effects of spinal anaesthesia includes opioids like fentanyl, morphine, clonidine, neostigmine, and more recently dexmedetomidine.²⁻⁴ However, most of these adjuvant drugs are associated with their own set of side effects, which limits their use. For example, opioid additives are associated with urinary retention, pruritus or delayed respiratory depression (more frequently with buprenorphine) while neostigmine is associated with a high incidence of nausea and vomiting.⁵

Dexmedetomidine, a new selective α-2-agonist, is a non-opioid which has been used intravenously for providing peri-operative supplementary sedation and analgesia. Data on its utility in central neuraxial blockade is limited with only a few studies on extensive medline and google search. Dexmedetomidine provides faster onset of both sensory and motor blockage, increased duration of sensory and motor blockade, with no significant side effects at smaller clinical doses being used.⁶⁻⁷ A few human studies have earlier shown that addition of intrathecal dexmedetomidine to hyperbaric bupivacaine in spinal anaesthesia increased the duration of analgesia without significant side effects. Yet, the ideal intrathecal dose of dexmedetomidine is still a matter of debate.⁶⁻⁷

It is well known that surgeries on femur bone are not only painful but sometimes are prolonged in duration that they run short of peri-operative or immediate post-operative analgesia. In the current study, we aimed to compare two different doses of dexmedetomidine added to heavy bupivacaine 0.5% intrathecally for fracture femur surgeries.

MATERIALS AND METHODS

In this prospective, double blind trial, after approval from institutional review board, 120 patients of ASA I & II status, between age 18-60 years and both genders, scheduled for fixation on fracture femur, during the study period from Jan 2014 to March 2015 (15 months) were enrolled for study. Written informed consent was obtained from all patients. Patients with any contraindication to spinal anaesthesia, hemodynamic instability,
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history of coagulopathy or associated head injury with GCS scores < 15 were excluded from the study.

Patients were evaluated in the pre-anaesthetic clinic prior to surgery and were explained about the procedure of spinal anaesthesia, visual analogue scale of pain and for their willingness to participate in the study.

On the day of surgery, the baseline VAS score was recorded in a pre-operative room in all the cases. Patients were randomized into two groups D1 and D2 using computer generated sequences. A two-operator technique was employed to maintain blinding where the operator preparing the drugs according to the group allocation was not involved in further patient management. In the operating room, standard monitoring that included pulse rate, 

\[ \text{SpO}_2 \], non-invasive blood pressure and ECG was attached and lactated Ringer’s solution of 500 ml was infused over 15 to 20 mins. With the patient in the sitting position a lumbar puncture was performed at L3-L4 inter space using midline approach by a 26-gauge Quincke needle. Cases in group D1 received 12.5 mg 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine while in group D2 received 12.5 mg 0.5% hyperbaric bupivacaine and 10 μg dexmedetomidine. Further interventions and monitoring were done by an investigator blinded to the group allocation. After spinal anaesthesia, all patients were placed in supine position and a level of T10 dermatome was achieved. Sensory level was assessed using loss of pinprick sensation in midline while modified Bromage scale was used to assess motor block. Time taken to achieve the desired effect was noted prior to surgery.

After surgery VAS scale was recorded before shifting the patient out of the operation theatre, at half hour intervals during 1st hour and thereafter at every hourly for next 8 hours and at 12 and 24 hours. Duration of two sensory level regression and regression of motor power to Bromage scale reading of 0 were also recorded. Duration of pain relief was measured from time of spinal anaesthetic injection to first request of rescue analgesics. Rescue analgesics used were inj. Diclofenac 75 mg BD. If satisfactory analgesia was not achieved than inj. Paracetamol 1 gm QID was added. The incidence of side effects like nausea, vomiting, bradycardia and hypotension were recorded in both the groups and managed as per the standard guidelines.

Statistical Analysis
To detect a 20% difference in the response rate among the groups with a minimum response of 50% estimated from initial pilot observations, with 90% power and 5% alpha error a sample size of 60 cases per group was required. The sample size was calculated using the power and sample size calculator of the Department of Biostatics, Vanderbilt University, US.

Analysis of data was done using SPSS® version 16 (Statistical Packages for the Social Sciences, Chicago, IL). Results are expressed as mean and standard deviation (SD), median and range or numbers. Quantitative data were compared using one-way analysis of variance (ANOVA), and independent samples t-test and qualitative data was analysed using chi square test. The P value of <0.05 was considered statistically significant.

RESULTS
A total of 120 ASA grade I, II patients were studied and the data collected was analysed. Patients were divided into two groups with 60 patients each. Both groups were comparable in terms of age, height, weight, ASA status, and duration of surgery as shown in [Table 1].

<table>
<thead>
<tr>
<th>Table 1: Patient Characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Height (cms)</td>
</tr>
<tr>
<td>Weight (Kgs)</td>
</tr>
<tr>
<td>ASA Status ASA I</td>
</tr>
<tr>
<td>ASA Status ASA II</td>
</tr>
<tr>
<td>Duration of surgery</td>
</tr>
</tbody>
</table>

Similarly other variables like baseline haemodynamic data and pain scores didn’t differ significantly in both the groups. Characteristics of sensory block were compared and no significant difference was noted in terms of highest level of sensory block achieved, time to achieve maximum sensory block and time of two-segment regression expressed in minutes [Table 2].
Table 2: Characteristics of Sensory Block

<table>
<thead>
<tr>
<th>Block Characteristics</th>
<th>D 1(Mean ± S.D.)</th>
<th>D 2(Mean ± S.D.)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest level of sensory block</td>
<td>T6-T10</td>
<td>T6-T8</td>
<td>NS</td>
</tr>
<tr>
<td>Time (min) to achieve sensory block</td>
<td>16.40 ± 4.45</td>
<td>15.40 ± 4.30</td>
<td>0.724</td>
</tr>
<tr>
<td>Time to achieve two-segment regression</td>
<td>107.30 ± 20.05</td>
<td>115.35 ± 25.05</td>
<td>0.051</td>
</tr>
<tr>
<td>Time to achieve maximum Bromage scale motor block</td>
<td>18.10 ±4.10</td>
<td>19.05± 4.35</td>
<td>0.065</td>
</tr>
<tr>
<td>Duration of regression of motor block</td>
<td>221.40 ± 55.60</td>
<td>231.40 ± 45.50</td>
<td>0.053</td>
</tr>
<tr>
<td>Time to first analgesic request (min)</td>
<td>210.30 ± 45.20</td>
<td>254.18 ± 40.55</td>
<td>0.029</td>
</tr>
<tr>
<td>Number of doses of diclofenac in the first 24 hours</td>
<td>84</td>
<td>68</td>
<td>0.037</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3</td>
<td>5</td>
<td>0.071</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5</td>
<td>5</td>
<td>--</td>
</tr>
</tbody>
</table>

Similarly, motor block characteristics, i.e. time to achieve maximal motor block and duration of regression to Bromage 0 showed no significant difference [Table 2]. However, when groups were compared in terms of time for requirement of first analgesic and total requirement of analgesic significant differences were observed. Time from lumbar puncture to request for first analgesic was 210± 45.20 minutes for the D1 group while it was 245± 40.55 for D2 group. Similarly, total no. of analgesic dose requirement is significantly less (68) in the D2 group as compared to D1 (84) [Table 2]. This proved that increasing the dose of dexmedetomidine increases the duration of analgesia and has a post operative analgesic sparing effect.

Heart rate and blood pressure values were comparable in both groups. In group D1 3 cases and 5 cases in group D2 received ephedrine for control of hypotension. In each group, 5 patients required Inj atropine for control of bradycardia during the perioperative period. Nausea was reported in 2 patients in group D1 and 1 patient in group D2 but vomiting was not reported. Similarly, there was no incidence of respiratory depression, severe sedation or itching requiring active medical attention.

**DISCUSSION**

Duration of action of intrathecally administered local anaesthetics is a major limiting factor for spinal anaesthesia. Various agents have been tried as adjuvant to prolong the effect of spinal anaesthesia. Dexmedetomidine, a dextro-isomer of medetomidine, is a highly selective α2-adrenoreceptor agonist. It has been shown that its affinity for α2-adrenoreceptor is about ten times higher than that of clonidine.\(^{[8, 9]}\) Activation of α2-adrenoreceptor has sympatholytic effect causing bradycardia, hypotension, sedation and analgesia.\(^{[10]}\)

Clonidine has already been shown to be an effective adjuvant to intrathecal local anaesthetics and opioids\(^{[10]}\). Comparative analysis of low dose dexmedetomidine (3 μg) with clonidine (30 μg) for intrathecal use has already been done by Kanazi et al\(^{[7]}\) and it was found to be equipotent to a ten times dose of clonidine. However, the use of dexmedetomidine as intrathecal adjuvant has not been studied extensively.

In the above study, patients in the group that received 10 μg dexmedetomidine had reduced postoperative pain scores and a longer analgesic duration than those who received 5 μg dexmedetomidine as adjuvant to spinal bupivacaine. This shows that the use of dexmedetomidine as intrathecal adjuvant causes statistically significant prolongation of duration of spinal anaesthesia, decreased postoperative pain and lesser analgesic requirements. Also, the effect appears to be dose dependent with 10 μg dexmedetomidine being more effective than 5 μg with no significant increase in incidence of hypotension or bradycardia as well as any other undesirable side-effects.

Dexmedetomidine acts on α2-adrenoreceptors located in the pre-synaptic C-fibres and postsynaptic dorsal horn neurons in the spinal cord. It acts on C-fiber inhibiting the release of pro-excitatory nociceptive transmitters i.e. glutamate & substance-P and hyper polarizes of post-synaptic dorsal horn neurons via G protein, mediated potassium channels resulting in analgesic effect.\(^{[11-12]}\)

No significant increase in incidence of undesirable side effects like hypotension, bradycardia and sedation was noted in our study. Lack of effect on blood pressure can be due to the fact that local anaesthetics decrease sympathetic outflow themselves resulting in reduction of blood pressure.
So intrathecal dexmedetomidine cannot cause further hypotension probably because sympathetic inhibition maximally achieved by bupivacaine. Lack of excessive sedation may be because CNS receptors responsible for this effect are spared from excessive doses of drug. However sedation may occur due to systemic absorption or upward migration of drug when used in higher doses as seen in study by Al-Ghanem et al who noted excessive sedation in 3 out of 25 patients. In our study, none of the patients reported excessive sedation or respiratory depression at 10 μg intrathecal dose of dexmedetomidine. Animal studies have already been performed to assess safety of dexmedetomidine for intrathecal use and showed no adverse neurotoxic effects. These studies also showed that epidural analgesic effect of α2-adrenoceptor agonist is directly related to their binding affinity.

Though, our current knowledge regarding use of dexmedetomidine as intrathecal adjuvant has been improved by this study, it has certain obvious limitations. Firstly, only healthy individuals ASA I and II were studied, so the effect on older patients with cardiovascular comorbidities needs to be evaluated in future trials. Moreover, increasing doses of dexmedetomidine can be added intrathecally in future studies to observe the its desirable and undesirable effects.

CONCLUSION

An Intrathecal dose of 10 μg dexmedetomidine can be safely used as an intrathecal adjuvant for increasing the duration of post-operative analgesia and decreasing post-operative analgesic requirements, compared to 5 μg dosing without any noticeable side effects.

REFERENCES


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