Prevention of Spinal Anesthesia Induced Hypotension in Elderly: Comparison of Prophylactic Atropine with Ephedrine

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Keywords: Spinal anesthesia; Hypotension; Atropine; Ephedrine

Introduction

Spinal blocks are major regional techniques with a long history of effective use for a variety of surgical procedures and pain relief. It produces sympathetic block, sensory analgesia and motor block, depending on dose, concentration, or volumes of local anesthetics, after insertion of a needle in plane of the neuraxis. Nevertheless, precipitous hypotension and difficulty in controlling the level of analgesia are major disadvantages of spinal block.

The most common serious side effects of spinal anesthesia are hypotension (33%) and bradycardia (13%) [1,2]. Systemic vasodilation induced by sympathetic blockade after spinal anesthesia (SA), resulting in venous pooling of blood and reduction in systemic vascular resistance, has been regarded as the predominant mechanism for hypotension. In addition, absence of significant reflex tachycardia after spinal anesthesia despite the presence of hypotension also play important role in development of hypotension [3]. This phenomenon may result from the blockade of cardio accelerator sympathetic fibers at T1 to T4, and possibly the “reverse” of the Bainbridge reflex. Caplan et al. [4] postulated that reduced atrial filling and unopposed vagal tone after SA produced a sufficient degree of bradycardia and hypotension, resulting in cardiac arrest. Present study hypothesized that the absence of reflex tachycardia is an important component in the pathogenesis of hypotension induced by SA in elderly patient in addition to effects of venous and arterial dilation. These complications are more common and more hazardous in elderly patients, as they may have decreased physiological reserve and compromised blood supply to various vital organs [5]. To deal with these problems currently various techniques are been using which include pre or co-loading of IV fluid, vasopressors, and physical methods such as table tilt, leg binders, compression devices and many more. However, none of these techniques are perfect in preventing such complication. So, there is always a search such of a technique or combinations to prevent spinal anesthesia induced hypotension and bradycardia.

Rational of choosing atropine in this study was that elderly have blunted Bainbridge reflex. So, the prophylactic use of atropine helps in preventing the blunted reflexes thus increasing heart rate and cardiac output, which finally increases blood pressure. Various studies also showed that ephedrine too improve hemodynamic parameter when used preoperatively in spinal anesthesia [6-9].

No published clinical study had compared the efficacy of prophylactic use of atropine or ephedrine preventing hypotension and bradycardia in elderly patient after spinal anesthesia. The primary outcome of the present study was to compare the heart rate and mean arterial pressure after spinal anesthesia with prophylactic use of atropine or ephedrine or placebo and secondary outcome included the need of vasopressor and occurrence of other adverse effects.
Methods

Institutional review board (IRB) at Tribhuvan University Teaching Hospital (TUTH) approved this prospective, randomized double blind controlled study, oral and written informed consent was obtained from the patients to enroll. The sample size was derived from the record of previous one-year where patients aged more than 60 years underwent urological surgeries under spinal anesthesia in the Department of Anesthesiology at TUTH. A size of 20 patients per group was required at power of 80% and type I error of 0.05. The inclusion criteria were elderly patient (age more than 60 years) scheduled for urological surgery under spinal anesthesia, with an American Society of Anesthesiologist physical status (ASA PS) I–II. Patient refusal or uncooperative patient for spinal anesthesia, contraindications to spinal block, arrhythmia such as atrial fibrillation, supraventricular tachycardia, heart block greater than 1st degree, left bundle branch block, hypertension (systolic blood pressure more than 140 mm Hg or diastolic blood pressure more than 90 mm Hg), unstable angina or cardiomyopathy, taking β-adrenergic blockers or any drugs that may alter normal response to study drugs were excluded from the study. After pre anesthetic evaluation, patients were randomized to one of the three groups using computer generated random number table to receive either normal saline (Group N) or atropine 0.6mg (Group A) or ephedrine 12 mg (Group E). All drugs were made in a volume of 2.5 ml in a similar looking syringe and the patient received the drugs one minute after the induction of spinal anesthesia as per the group allocation.

Patients were premedicated with tab midazolam 7.5 mg per oral two hours before surgery. In the preanesthetic preparation room, all patients were preloaded with normal saline (NS) 10 ml/kg 20 minutes before the induction of spinal anesthesia. In operating room, patients were monitored for baseline heart rate, non-invasive blood pressure, oxygen saturation and electrocardiogram till completion of surgery. Sub arachnoid block was done at L3-L4 space with 2.5 ml of 0.5% hyperbaric bupivacaine in sitting position and were immediately made to lie in supine position. After one minute of spinal anesthesia, one of the study drugs (either atropine 0.6mg or ephedrine 12.5mg or placebo (normal saline) was injected intravenously. MAP and HR were recorded at 0 (baseline), 1,5,10, 20,30,40,50 and 60 minutes following the administration of study drugs respectively.

Clinically, significant hypotension was defined as systolic blood pressure of <90 mm Hg and if developed treated with inj. mephentermine 6 mg IV. Inj. phenylephrine 50 mcg IV was administered as a rescue drug if more than 30 mg of inj. mephentermine was required. Bradycardia (HR<50 bpm) was treated with atropine 0.6mg or ephedrine 12.5mg or placebo (normal saline) was injected intravenously. Tachycardia (HR>140/min) was treated with bolus IV esmolol 10 mg. Hypertension (SBP more than 160 mmHg or DBP more than 100 mmHg) was treated with bolus IV esmolol 10 mg and repeated till corrected.

Amount of vasopressor (mephentermine or phenylephrine) required, sensory level achieved at 15 min of spinal anesthesia, presence of intraoperative angina and intra/postoperative confusion and other side effects were recorded till 6 hours postoperative.

Data were collected as per the proforma. For the analysis of the data Statistical Package for the Social Sciences (SPSS) 17 was used. For statistical analysis, Analyses Of Variance (ANOVA) with Bonferroni multiple comparisons, Mann Whitney U test, Kruskal -Wallis H test were used. For comparing categorical variables chi square test was used. For those variables satisfying normality assumption, ANOVA with Bonferroni comparisons were carried out. For other variable not satisfying normality assumption Kruskal-Wallis H test was used. For variables observed significantly different by Kruskal-Wallis H test, the pair wise comparison were made using Mann Whitney U test. P values <0.05 were considered as statistically significant.

Results

All sixty patients enrolled completed the study. Demographic data (Age, Weight, ASA PS and Diagnosis) in all three groups were comparable as shown in Table 1. There were no differences regarding demographics, type of surgeries and duration of surgery in all three groups. The types of surgeries were transurethral resection of prostate under spinal anesthesia either for prostatic enlargement (BEP) or Carcinoma of Urinary bladder.

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>p</th>
<th>Group</th>
<th>E</th>
<th>p</th>
<th>Group N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>70.00 ± 7.90</td>
<td>68.65 ± 8.09</td>
<td>69.85 ± 8.09</td>
<td>0.79</td>
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</tr>
<tr>
<td>Weight (Kg)</td>
<td>60.00 ± 10.31</td>
<td>60.70 ± 5.38</td>
<td>59.50 ± 6.62</td>
<td>0.91</td>
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<tr>
<td>Baseline HR</td>
<td>73.60 ± 10.30</td>
<td>71.35 ± 7.70</td>
<td>71.35 ± 7.70</td>
<td>0.75</td>
<td></td>
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<tr>
<td>Baseline MAP</td>
<td>97.88 ± 6.70</td>
<td>92.38 ± 9.23</td>
<td>92.38 ± 9.23</td>
<td>0.1</td>
<td></td>
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<tr>
<td>Duration of Surgery</td>
<td>70.85 ± 7.92</td>
<td>68.90 ± 9.40</td>
<td>72.55 ± 6.45</td>
<td>0.46</td>
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</tbody>
</table>

Data described as mean ± SD; *p<0.05 considered statistically significant. MAP: Mean Arterial Pressure; HR: Heart Rate; SD: Standard Deviation

As compared to the baseline, mean heart rate was increased in Group A and Group E at 1, 5, 10, 15, 20 and 30 minutes (Table 2). Maximum heart rate in Group A was 89.30 ± 14.62 bpm at 5 minute and in Group E was 87.55 ± 13.75 bpm at 5 minute. In contrast, HR significantly decreased in Group N at 30, 40, 50 and 60 minutes with minimum mean HR was 65.40 ± 11.34 bpm. In-group N, 40% of the patient required atropine for the treatment of bradycardia, which was statistically significant (p=0.01) (Table 3).

**Table 1: Demographic data.**

**Table 2: Heart rate distribution.**

**Table 3: Blood pressure distribution.**
As compared to baseline, MAP didn’t change significantly in Group A except at one minute whereas in group E, MAP significantly increased at one minute but significantly decreased in rest of the period (Table 3). But the decreased in MAP in Group E was not clinically significant requiring treatment (Table 4). However, in-group N, MAP significantly decreased all the times (Table 3) requiring treatment in 40% cases (Table 4).

### Table 2: Comparison of mean HR with baseline in each group.

As compared to baseline, MAP didn’t change significantly in Group A except at one minute whereas in group E, MAP significantly increased at one minute but significantly decreased in rest of the period (Table 3). But the decreased in MAP in Group E was not clinically significant requiring treatment (Table 4). However, in-group N, MAP significantly decreased all the times (Table 3) requiring treatment in 40% cases (Table 4).

<table>
<thead>
<tr>
<th>Group</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
<th>Group D (n=20)</th>
<th>Group E (n=20)</th>
<th>Group F (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>97.88 ± 6.70</td>
<td>98.95 ± 4.97</td>
<td>92.38 ± 9.23</td>
<td>91.10 ± 11.30</td>
<td>76.92 ± 11.60</td>
<td>76.30 ± 9.56</td>
</tr>
</tbody>
</table>

Data described as mean ± SD; *p<0.05 considered statistically significant. MAP: Mean Arterial Pressure; BL: Baseline; SD: Standard Deviation

### Table 3: Comparison of mean MAP with baseline in each group.

<table>
<thead>
<tr>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
<th>Group D (n=20)</th>
<th>Group E (n=20)</th>
<th>Group F (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP 1</td>
<td>103.17 ± 8.87</td>
<td>101.12 ± 10.69</td>
<td>92.38 ± 9.23</td>
<td>91.10 ± 11.30</td>
<td>76.92 ± 11.60</td>
</tr>
<tr>
<td>MAP 2</td>
<td>98.80 ± 8.27</td>
<td>93.92 ± 10.84</td>
<td>81.43 ± 13.68</td>
<td>76.92 ± 11.60</td>
<td>76.30 ± 9.56</td>
</tr>
<tr>
<td>MAP 3</td>
<td>97.00 ± 8.16</td>
<td>93.87 ± 11.83</td>
<td>85.00 ± 10.79</td>
<td>85.00 ± 10.79</td>
<td>76.30 ± 9.56</td>
</tr>
<tr>
<td>MAP 4</td>
<td>95.73 ± 11.68</td>
<td>90.25 ± 11.52</td>
<td>82.40 ± 10.48</td>
<td>82.40 ± 10.48</td>
<td>76.30 ± 9.56</td>
</tr>
<tr>
<td>MAP 5</td>
<td>94.88 ± 10.70</td>
<td>89.13 ± 10.93</td>
<td>82.92 ± 10.30</td>
<td>82.92 ± 10.30</td>
<td>76.30 ± 9.56</td>
</tr>
<tr>
<td>MAP 6</td>
<td>96.30 ± 9.51</td>
<td>91.33 ± 9.86</td>
<td>82.60 ± 10.81</td>
<td>82.60 ± 10.81</td>
<td>76.30 ± 9.56</td>
</tr>
<tr>
<td>MAP 7</td>
<td>94.40 ± 9.41</td>
<td>92.92 ± 10.73</td>
<td>84.42 ± 9.84</td>
<td>84.42 ± 9.84</td>
<td>76.30 ± 9.56</td>
</tr>
<tr>
<td>MAP 8</td>
<td>95.10 ± 9.36</td>
<td>92.82 ± 9.51</td>
<td>83.20 ± 9.40</td>
<td>83.20 ± 9.40</td>
<td>76.30 ± 9.56</td>
</tr>
</tbody>
</table>

Data described as mean ± SD; *p<0.05 considered statistically significant. MAP: Mean Arterial Pressure; BL: Baseline; SD: Standard Deviation

### Table 4: Intra operative events.

Intra group comparison, MAP was significantly high at atropine group compared to ephedrine and placebo group at 1 minute. Whereas at 5, 10, 15, 30, 40, 50, and 60 minute MAP was comparable between Group A and group E but in placebo group MAP was significantly low compared to other groups (Figure 2).

Intraoperatively, 60% patient developed hypotension (p=0.01) and 40% developed bradycardia (p=0.01) in placebo group requiring treatment, which was statistically significant (Table 4). None of the patients in any group developed side effects like intra operative angina and intra/postoperative confusion till 6 hrs postoperatively. No other side effects were detected in any of the groups.

### Discussion

The most common serious side effects from spinal anesthesia are hypotension and bradycardia which include pre or co-loading of IV fluid, vasopressors, and physical methods such as table tilt, leg binders, and compression devices [12-18]. However, a Cochrane review concluded that none of these techniques alone is effective and...
suggested that the future research be directed towards a combination of interventions [15]. This study aimed to prevent the spinal anesthesia induced hypotension with combination of preloading with normal saline 10 ml/kg and pretreatment with either IV atropine or ephedrine.

Figure 2: Intra group comparison of trend MAP. *p value significant (<0.05) in Group A vs. Group N, Group E vs. Group N and Group E vs. Group A; #p values significant (<0.05) in both group A vs. N and group E vs. group N; ¶p value significant (0.05) in only in group A vs. group N.

Atropine [19,20] is an esters of an aromatic acid combined with an organic base. It competitively blocks acetylcholine binding to its receptor and prevents receptor activation thus cellular effects of acetylcholine are inhibited. In general, atropine lowers the parasympathetic nervous system and increase heart rate via abolishing the vagal tone acting on M2 receptor at heart.

Ephedrine [19,20] is a sympathomimetic amine. The principal mechanism of its action relies on its indirect stimulation of the adrenergic receptor system by increasing the activity of noradrenaline at the post-synaptic α- and β-receptors. Ephedrine is commonly used to treat the hypotension that may occur with spinal anesthesia.

The present study showed that the incidence of bradycardia was significantly high at various time [Table 2] in placebo group and required treatment (p=0.01) compared to other groups. It was also observed in placebo group that low heart rate persist even in later half of the surgery (at 30, 40, 50 and 60). The possible explanation of persistence of low HR may be the result of blockade of cardiac accelerator sympathetic fibers at T1 to T4 and the “reverse” of the Bainbridge reflex persists longer in elderly. Compared to baseline heart rate was high in atropine [maximum reaching 88.95 ± 14.62 (p=0.00*)] and ephedrine [maximum 87.55 ± 13.75 (p=0.00*)] group at 5 minute, which corresponds to the peak effect of the IV atropine and IV ephedrine. But intergroup comparison between atropine and ephedrine group HR changes over time were comparable. Though HR was high statistically, clinically comparable and only one patient in atropine group required treatment for tachycardia, which was not significant (p=0.48). Similarly, MAP was also lower in placebo group at most of the time compared to other group. In contrast to atropine group, ephedrine group had significant low MAP compared to its baseline, which implied atropine was better in prevention of hypotension than ephedrine. However, both were effective compared to placebo group. In present study, 60% patient in placebo group, 5% in ephedrine group and 5% patient in atropine group required mephentermine for the treatment of hypotension. Use of mephentermine was significant (p=0.01) in placebo group compared to ephedrine or atropine group. While comparing ephedrine with atropine group use of mephentermine was not statistically significant.

Possible explanation for the reduced incidence of hypotension and bradycardia with the prophylactic use of atropine or ephedrine may be the help in preventing the blunted Bainbridge reflex thus increasing heart rate and cardiac output. Moreover, ephedrine increases systemic vascular resistant by increasing norepinephrine in the post synaptic membrane and helps in maintaining blood pressure even after spinal anesthesia.
All patients were observed for 6 hours in postoperative ward for the study. Actions of atropine and ephedrine do not last more than 6 hours. So, the postoperative observation period was chosen for 6 hours. None of the groups developed other side effects and complications during intraoperative or postoperative periods.

In summary, hypotension and bradycardia after induction of spinal anesthesia were common in elderly patients. The use of IV ephedrine or atropine one minute after the induction of spinal anesthesia in elderly patient was beneficial in maintaining hemodynamic stability. Although, the incidence of tachycardia was high in atropine group and ephedrine group the incidence of clinically significant tachycardia (HR>140 bpm) were comparable among all the three groups. None of the patients in all groups developed other side effects. So, the study suggests prophylactic IV ephedrine or atropine can be safely used in elderly patient for the prevention of spinal anesthesia induced hypotension.

Limitations

Amount of blood loss, which could influence the hemodynamic parameters, was not recorded in the study. For the measurement of blood pressure oscillatory noninvasive blood pressure methods was used, invasive blood pressure monitoring method would have been better to monitor real time blood pressure. Only urological surgeries (TURP, CA UB) were taken for the study, which require only lower thoracic block for surgery. Study population might not be the actual representative of the SA induced hypotension associated with higher blocks more than T8.

Conclusions

The use of prophylactic IV atropine or IV ephedrine after one minute of induction of spinal anesthesia reduces the incidence and severity of the spinal anesthesia induced hypotension and bradycardia in elderly patients without clinically significant side effects. The study also concluded that atropine has better profile than ephedrine maintaining hemodynamics in elderly patient.

Recommendation

Pretreatment with IV atropine (0.6 mg) or IV ephedrine (12 mg) one minute after induction of spinal anesthesia is recommended in elderly patients with low baseline heart rate to maintain intraoperative hemodynamic stability. However, routine use of these drugs in young patients and in patients with ischemic heart disease and cardiac arrhythmias need further study.

References