Journal of Anesthesia & Clinical Research

Sigdel et al., J Anesth Clin Res 2015, 6:8
DOI: 10.4172/2155-6148.1000557

Research Article Open Access

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

Shailendra Sigdel*, Anil Shrestha and Roshana Amatya

Deaprtment of Anesthesiology, Manmohan Cardiothoracic Vascular and Transplant Center, Institute of Medicine, Tribhuvan University, Maharajgunj, Kathmandu, Nepal

***Corresponding author:** Shailendra Sigdel, Anesthesiology, Manmohan Cardiothoracic Vascular and Transplant Center, Institute of Medicine, Tribhuvan University, Maharajgunj, Kathmandu, Nepal, Tel: +9779851123474; E-mail: sigdelshailendra@gmail.com

Received date: Jul 25, 2015, **Accepted date:** Aug 25, 2015, **Published date:** Aug 31, 2015

Abstract

Background: Spinal anesthesia induced hypotension is more common and hazardous in elderly, as they have decreased physiological reserve and compromised blood supply to various vital organs. Reversal of the blunted reflexes of tachycardia following hypotension in elderly with atropine or ephedrine may help in prevention of hypotension.

Methodology: Present study is a prospective, randomized, double blind, controlled trial where sixty ASAPS I-II patients undergoing urological surgeries were assigned to receive either IV normal saline (placebo) or IV atropine 0.6 mg or IV ephedrine 12 mg one minute after induction of spinal anesthesia. Heart rate (HR), mean arterial pressure (MAP), requirement mephentermine and phenylephrine and side effects profile were studied were studied. Hemodynamic parameters were compared with baseline in each and among the groups.

Results: The patients were comparable with demographic data, baseline hemodynamic parameters and duration of surgery. Compared to baseline, trend of mean HR and MAP significantly dropped in placebo in most of the times (p group (5%)].

Conclusion: Administration of intravenous atropine 0.6 mg or IV ephedrine (12 mg) one min after induction of spinal anesthesia in elderly patient is safe and effective in the prevention of spinal anesthesia induced hypotension and bradycardia, requirement of vasopressors decreased without clinically significant side effects.

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 aesthesia [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. phenylepherine 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 0.6 mg. 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 Whiteney 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 Whiteney 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 prosthetic enlargement (BEP) or Carcinoma of Urinary bladder.

	Group A (n=20)	Group E (n=20)	Group N (n=20)	p value
Age (yrs.)	70.00 ± 7.90	68.65 ± 8.09	69.85 ± 8.09	0.79
Weight (Kg)	60.00 ± 10.31	60.70 ± 5.38	59.50 ± 6.62	0.91
Baseline HR	73.60 ± 10.30	71.35 ± 7.70	71.35 ± 7.70	0.75
Baseline MAP	97.88 ± 6.70	92.38 ± 9.23	92.38 ± 9.23	0.1
Duration of Surgery	70.85 ± 7.92	68.90 ± 9.40	72.55 ± 6.45	0.46
Data described as mean ± SD; *p<0.05 considered statistically significant. MAP: Mean Arterial Pressure; HR: Heart Rate; SD: Standard Deviation				

Table 1: Demographic data.

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 bmp 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).

	Group A (n=20)	p	Group E (n=20)	p	Group N	p value
HR BL	73.60 ± 10.30		71.40 ± 5.95		71.35 ± 7.70	
HR1	83.35 ± 14.13	0.00*	80.05 ± 12.46	0.00*	71.45 ± 9.74	0.88
HR5	88.95 ± 14.62	0.00*	87.55 ± 13.75	0.00*	68.95 ± 0.07	0.15
HR10	85.40 ± 13.18	0.00*	84.15 ± 11.16	0.00*	67.60 ± 9.95	0.08*
HR15	83.80 ± 14.35	0.00*	81.40 ± 11.65	0.00*	68.05 ± 9.82	0.11
HR20	82.30 ± 13.56	0.00*	79.25 ± 11.49	0.00*	69.00 ± 3.95	0.25
HR30	80.95 ± 13.53	0.01*	77.80 ± 9.80	0.00*	65.95 ± 1.03	0.01*
HR40	6.20 ± 13.31	0.47	73.50 ± 10.78	0.54	65.40 ± 1.34	0.01*

HR50	76.30 ± 9.56	0.25	71.95 ± 10.61	0.97	65.80 ± 0.66	0.04*
HR 60	76.20 ± 12.91	0.5	74.30 ± 9.97	0.12	66.25 ± 0.47	0.02*

Data described as mean ± SD; *p<0.05 considered statistically significant. HR: Heart Rate, BL: Baseline; SD: Standard Deviation

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).

Group A	Group A (n=20)	p	Group E (n=20)	p	Group N (n=20)	p
MAP BL	97.88 ± 6.70		98.95 ± 4.97		92.38 ± 9.23	
MAP 1	103.17 ± 8.87	0.01*	101.12 ± 10.69	0.05*	91.10 ± 11.30	0.24
MAP 5	99.80 ± 10.74	0.31	96.85 ± 9.12	0.14	76.92 ± 11.60	0.00*
MAP 10	98.80 ± 8.27	0.81	93.92 ± 10.84	0.03*	81.43 ± 13.68	0.00*
MAP 15	97.00 ± 8.16	0.56	93.87 ± 11.83	0.03*	85.00 ± 10.79	0.00*
MAP 20	95.73 ± 11.68	0.37	90.25 ± 11.52	0.00*	82.40 ± 10.48	0.00*
MAP 30	94.88 ± 10.70	0.12	89.13 ± 10.93	0.00*	82.92 ± 10.30	0.00*
MAP 40	96.30 ± 9.51	0.48	91.33 ± 9.86	0.00*	82.60 ± 10.81	0.00*
MAP 50	94.40 ± 9.41	0.09	92.92 ± 10.73	0.01*	84.42 ± 9.84	0.00*
MAP 60	95.10 ± 9.36	0.13	92.82 ± 9.51	0.00*	83.20 ± 9.40	0.00*

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.

	Group A(n=20)	Group E (n=20)	Group N (n=20)	p value
Mephentermine used	1 (5%)	1 (5%)	12 (60%)	0.01*
Bradycardia	0	0	8 (40%)	0.01*
Tachycardia	1 (5%)	0 (0%)	0 (0%)	0.48
Other adverse effects	0	0	0	

Data described as number (percentage); *p<0.05 considered statistically significant.

Table 4: Intra operative events.

Intragroup comparison, heart rate was significantly high in atropine group compared to ephedrine and placebo group at 1, 5, 10 and 15 minutes. Whereas at 20, 40, 50 and 60 minutes HR were comparable between ephedrine and atropine group but in placebo group it was significantly low compared to other groups (Figure 1).

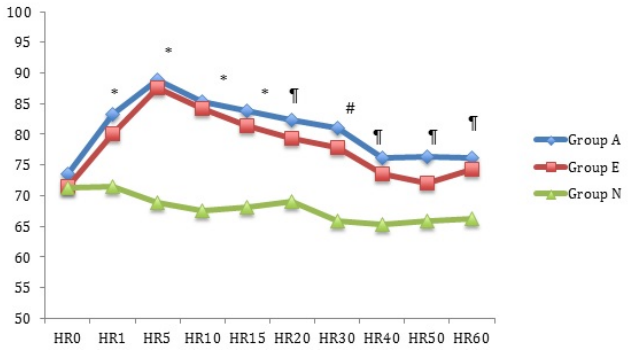

Figure 1: Intra group comparison of trend HR. *p value significant (<0.05) in Group A vs. Group N, Group E vs. Group N and Group E vs. Group A; #p values significant (<0.05) in both group A vs. N and group E vs. group N; ¶p value significant (0.05) in only in group A vs. group N.

Intra group comparison, MAP was significantly high in 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 [1,2] and closed claims surveys of 40,000-550,000 spinal anesthetics indicate an incidence of cardiac arrest from 0.04-1/10,000 [5,10]. Risk factors for hypotension block are height T5 or greater, age 40 yrs or greater, baseline systolic blood pressure less than 120 mmHg, and spinal puncture above L3-L4. Risk factors for development of bradycardia include baseline heart rate less than 60 bpm, ASA PS I, use of β-adrenergic blockers, prolonged PR interval on electrocardiogram, and block height T5 or greater [1,11].

Currently various techniques are been using for the prevention of 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.

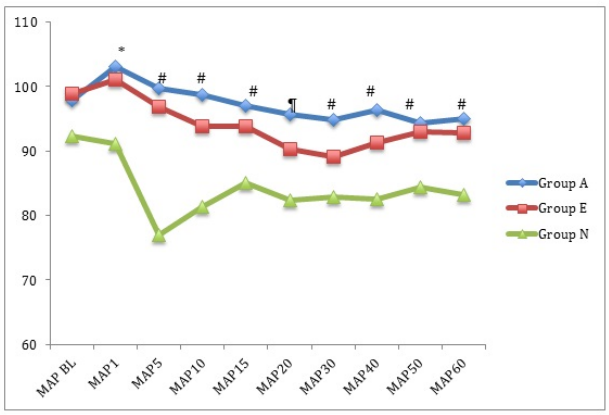

Figure 2: Intra group comparison of trend MAP. *p value significant (<0.05) in Group A vs. Group N, Group E vs. Group N and Group E vs. Group A; #p values significant (<0.05) in both group A vs. N and group E vs. group N; ¶p value significant (0.05) in only in group A vs. group N.

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 activity of all muscles and glands regulated by 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 results of blockade of cardio 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. This indicated that both incidence and severity of hypotension were greater in placebo group\compared to other groups. The findings were similar to various other studies. Hwee et al. [21] demonstrated that IV atropine after a crystalloid infusion in patients undergoing SA could increase HR very quickly in a dose-dependent manner and decrease the incidence of significant hypotension also in a dose-dependent manner. Similarly, PUN Nze [22] demonstrated both the incidence and severity of hypotension were reduced in parturient undergoing cesarean section under spinal anesthesia with use of prophylactic intravenous bolus of atropine and concluded that the intravenous atropine may be a useful supplement to the existing methods in preventing hypotension induced by spinal anesthesia. However, when IM atropine was used, Hirabayashi et al. [23] did not demonstrate any beneficial effect in hemodynamic stability during SA because the absorption of IM atropine may be unpredictable, and the onset may have been too slow in comparison to the onset of hypotension after SA. Another anticholinergic agent, glycopyrrolate, when administered IV after SA increased HR and reduced the severity of hypotension [24] in women presenting for elective cesarean section at term and concluded that glycopyrrolate reduced the severity of hypotension after SA, as evidenced by reduced ephedrine requirements (p=0.002).

Similarly, Sternlo et al. [7] had investigated the efficacy of IM ephedrine in elderly patients undergoing hip arthroplasty under spinal anesthesia with plain bupivacaine and concluded that ephedrine administered in the paravertebral muscles immediately after spinal anesthesia was a simple and effective means of reducing the incidence of hypotensive episodes in the elderly patient. Katie et al. [8] investigated two hundred women, ASA physical status I or II undergoing lower abdominal surgery concluded that oral ephedrine premedication (30 minutes before spinal anesthesia) was a simple and effective way of reducing the incidence of hypotension compared to control group (p<0.01). Kohki et al. [25] studied prophylactic use of another vasopressor (IM phenylephrine) on hyperbaric tetracaine spinal anesthesia-induced hypotension in 90 elderly patients (age>65 years) undergoing surgery for hip fracture. The incidence of hypotension was significantly lower in the patients who received phenylephrine 1.5 mg or 3 mg than in the controls, both in the normotensive and hypertensive groups (p= 0.01). In a quantitative, systematic review of seven randomized controlled trials analyzed by Lee et al [9] comparing ephedrine with phenylephrine for the prevention and treatment of maternal hypotension during spinal anesthesia for cesarean delivery there was no significant difference between phenylephrine and ephedrine (relative risk [RR] of 1.00; 95% confidence interval (0.96-1.06).

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

1. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R (1992) Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology 76: 906-916.
2. Arndt JO, Bömer W, Krauth J, Marquardt B (1998) Incidence and time course of cardiovascular side effects during spinal anesthesia after prophylactic administration of intravenous fluids or vasoconstrictors. Anesth Analg 87: 347-354.
3. Dobson PM, Caldicott LD, Gerrish SP, Cole JR, Channer KS (1994) Changes in haemodynamic variables during transurethral resection of the prostate: comparison of general and spinal anaesthesia. Br J Anaesth 72: 267-271.
4. Caplan RA, Ward RJ, Posner K, Cheney FW (1988) Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. Anesthesiology 68: 5-11.
5. Auroy Y, Narchi P, Messiah A, Litt L, Rouvier B, et al. (1997) Serious complications related to regional anesthesia: results of a prospective survey in France. Anesthesiology 87: 479-486.
6. Eroglu F, Yavuz L, Ceylan BG, Sevin G, Soyupek S (2003) Prophylactic effects of systemic oral ephedrine in spinal anesthesia-induced hypotension during transurethral prostatectomy. Scand J Urol Nephrol 37: 145-150.
7. Sternlo JE, Rettrup A, Sandin R (1995) Prophylactic i.m. ephedrine in bupivacaine spinal anaesthesia. Br J Anaesth 74: 517-520.
8. Kafle SK, Malla SM, Lekhak BD (1994) Prophylactic oral ephedrine reduces the incidence of hypotension after subarachnoid block. Can J Anaesth 41: 1091-1093.
9. Lee A, Ngan Kee WD, Gin T (2002) A Quantitative, Systematic Review of Randomized Controlled Trials of Ephedrine versus Phenylephrine for the Management of Hypotension during Spinal Anesthesia for Cesarean Delivery. Anesth Analg 94: 920-926.
10. Aromaa U, Lahdensuu M, Cozanitis DA (1997) Severe complications associated with epidural and spinal anaesthesias in Finland 1987-1993. A study based on patient insurance claims. Acta Anaesthesiol Scand 41: 445-452.
11. Liu S, Paul GE, Carpenter RL, Stephenson C, Wu R (1995) Prolonged PR interval is a risk factor for bradycardia during spinal anesthesia. Reg Anesth 20: 41-44.
12. Sharma SK, Gajraj NM, Sidawi JE (1997) Prevention of hypotension during spinal anesthesia: a comparison of intravascular administration of hetastarch versus lactated Ringer's solution. Anesth Analg 84: 111-114.
13. Brooker RF, Butterworth JFt, Kitzman DW, Berman JM, Kashtan HI, (1997) Treatment of hypotension after hyperbaric tetracaine spinal anesthesia: A randomized, double-blind, cross-over comparison of phenylephrine and epinephrine. Anesthesiology 86: 797-805.
14. Critchley LA, Conway F (1996) Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol. Br J Anaesth 76: 734-736.
15. Emmett RS, Cyna AM, Simmons SW (2002) Techniques for preventing hypotension during spinal anaesthesia for caesarean section. The Cochrane Database of Systematic Reviews 3: CD002251.
16. Coe AJ, Revanäs B (1990) Is crystalloid preloading useful in spinal anaesthesia in the elderly? Anaesthesia 45: 241-243.
17. McCrae AF, Wildsmith JA (1993) Prevention and treatment of hypotension during central neural block. Br J Anaesth 70: 672-680.
18. Rout CC, Rocke DA, Gouws E (1993) Leg elevation and wrapping in the prevention of hypotension following spinal anaesthesia for elective caesarean section. Anaesthesia 48: 304-308.
19. Katzung BG, Trevor AJ (2006) Basic and Clinical Pharmacology (10thedn.) McGraw-Hill, New York (NY).
20. Stoelting RK, Hiller SC (2006) Pharmacology and physiology practice in anaesthesia practice (4thedn.) Lippincott Williams and Wilkins, Baltimore (MD).
21. Lim HH, Ho KM, Choi WY, Teoh GS, Chiu KY (2000) The use of intravenous atropine after a saline infusion in the prevention of spinal anesthesia-induced hypotension in elderly patients. Anesth Analg 91: 1203-1206.
22. PUN Nze (2003) Effect of Pre-medication with Atropine on the Blood Pressure of Parturient Undergoing Caesarian Section under Spinal Anaesthesia. Orient Journal of Medicine 15: 1-4.
23. Hirabayashi Y, Saitoh K, Fukuda H, Shimizu R (1994) [Atropine has little significance as a premedication for spinal anesthesia]. Masui 43: 306-310.
24. Ure D, James KS, McNeill M, Booth JV (1999) Glycopyrrolate reduces nausea during spinal anaesthesia for caesarean section without affecting neonatal outcome. Br J Anaesth 82: 277-279.
25. Kohki N, Michiaki Y, Keiichi O, Akiyoshi N (2002) Prophylactic IM Small-Dose Phenylephrine Blunts Spinal Anesthesia-Induced

Hypotensive Response During Surgical Repair of Hip Fracture in the Elderly. Anesth Analg 95: 751-756.